PROCEEDINGS OF THE MIM AFRICAN MALARIA CONFERENCE

Held in conjunction with the Southern African Malaria Initiative and the Roll Back Malaria Project of the World Health Organisation

CONFERENCE MIM AFRICAINE SUR LE PALUDISME

en association avec la Conférence du Sud de l'Afrique sur le Paludisme

et le projet 'Roll Back Malaria' de l'Organisation Mondiale de la Santé

International Convention Centre

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PREFACE

On 14-19 March 1999 a remarkable gathering of malaria experts took place at the International Convention Centre in Durban, South Africa. This 'African Malaria Conference' was organised under the umbrella of the Multilateral Initiative on Malaria (MIM) and reflected an invigorated international commitment to tackle the serious and growing burden of malaria disease in Africa. The unique event was the product of many partners working in co-operation towards a shared goal that could not have been achieved by individual action alone. In particular, the UK-based Wellcome Trust, as the co-ordinator of MIM during 1998, worked in close partnership with the South African Medical Research Council, Durban, and with many organisations and individuals from across Africa, Europe and the United States. This spirit of cooperation reflected the prevailing climate, in which there was an emerging realisation of the benefits of international partnerships to tackle scientific problems of a major scale.

The Conference was prioritised by MIM to address the need for a forum that could bring together malaria scientists, control experts and health professionals working at widely-separated locations across sub-Saharan Africa. Such a forum was intended to promote interactions amongst African scientists to enable sharing of information and experiences, and to link scarce, fragmented resources together for maximal impact. A further key goal was to strengthen partnerships between the research and control communities. In aiming to fulfil this goal the MIM Conference built upon the accomplishments of the Southern African Malaria Congress held in Mozambique in 1997. The MIM Conference was the first time, however, that bridging of African malaria research and implementation activities had been attempted on a continent-wide basis.

Despite a conviction that the Conference would be a significant event, we did not anticipate the full extent of the enthusiasm and commitment of the African and international malaria communities. With a final count of over 850 delegates, this was the largest gathering of malaria experts ever to take place on African soil, and probably the largest ever. The high standard of talks and posters from the strong African representation is a testament to the progress that has been made in encouraging the emergence of a vigorous research community on the continent. Such a Conference probably could not have taken place ten years ago, and the tangible excitement generated by so many delegates from different regions of Africa gathered in one place at the opening ceremony was moving to witness. We were also quite overwhelmed by the enthusiastically positive comments of many participants. Durban provided a fitting location, not only because of the pleasant climate, the proximity of the Indian Ocean and the state of the art facilities at the International Convention Centre, but also because the region was historically a malarious area – providing an optimistic note and a reminder that success against malaria is feasible.

The MIM Conference was distinct from other scientific meetings in that its focus was on the problem of malaria in Africa. The programme reflected the breadth of malaria research ongoing in African laboratories, extending from molecular biology and immunology through to field trials and epidemiology. However, the scientific content had an emphasis on the more applied studies that particularly characterise current African research. For example there were sessions dedicated to the management of severe malaria, malaria in pregnancy, health information systems and the economics of malaria – the latter areas in particular are rarely given major attention in standard scientific meetings. Contributions from international scientists were also important in linking African studies to research programmes in Europe and North America.

The MIM Conference was timely in being able to play an important role in galvanising a variety of malaria initiatives that had been actively developed in both the research and control communities in the preceding few years. In particular, the Conference included progress reports on research activities under MIM, and embraced plans for the Roll Back Malaria movement of WHO, which had recently been established to lead global plans to

control malaria. Discussions amongst international funders and stakeholders were significant in firming up and driving forward new plans. Importantly, the next steps for MIM were agreed upon at a partners' meeting held after the Conference. These included the nomination of the Fogarty International Center of the US National Institutes of Health as the new MIM coordinator to take over from the Wellcome Trust in 1999.

As highlighted in the closing speech of Dr Zweli Mkize (MEC for Health in KwaZulu-Natal Province), the Conference was also opportune with respect to signing of agreements by South Africa, Swaziland and Mozambique for regionally co-ordinated activities to control malaria – a significant and exciting advance in co-operation between bordering countries to control a disease that does not respect political boundaries.

The Conference would not have been possible without the quite remarkable collective commitment of 25 funding organisations and 10 commercial companies to which a special debt of gratitude is owed. Sponsorship was raised for over 300 delegates, mostly from Africa, and this was critical to the success of the event. Notable amongst the sponsors were the US National Institutes for Health, The Wellcome Trust, Zeneca, AgrEvo, the US Agency for International Development and the World Health Organisation. Nevertheless, each sponsor (listed later) made a very important contribution and credit is due to them all.

Organisation of the Conference was very much a team effort and we would like to express our immense appreciation to all of the organisers and sponsors whose vision and contributions helped to make the event a resounding success. Members of the Steering and Organising Committees, Session Co-ordinators, chairpersons and rapporteurs put in long hours to plan and implement the Conference agenda. It was a pleasure and a privilege to work with such an able and committed international team. The Meetings and Travel Department of the Wellcome Trust led by the irrepressible Jilly Steward deserves special mention for ensuring that sponsored delegates were booked onto flights, and into hotel accommodation and were generally looked after well while they were in Durban. Carrin Martin of the MRC in Durban also deserves particular recognition as the person responsible for crafting the memorable evening entertainments in conjunction with sponsors. These events provided wonderful venues to establish new contacts and strengthen existing ones. We are also indebted to the rest of the teams in Durban and in London – each individual made a key contribution.

The presence of both the research and control communities in Durban created a unique environment to try to define outstanding research needs, where major gaps in data to underpin control programmes exist. It also provided an opportunity to highlight research results with immediate applications to control activities, and to identify capacity needs in Africa. While some research areas were evidently active and advancing well, it was clear that some other disciplines that are critical to inform effective planning and implementation of health programmes were still in their infancy and required greater attention to enable them to advance and develop a stronger critical mass.

These Conference Proceedings provide a record of the high quality presentations, lively discussions, conclusions and recommendations from Durban. We hope that they also convey something of the sense of occasion of the Conference and the atmosphere of excitement and optimism that it generated. The plenary speeches and breakout sessions at the Conference were truly representative of current malaria research activity across sub-Saharan Africa, with input from external collaborating partners. As such the Proceedings, combined with the Conference abstracts, are an enormously valuable resource for those involved in planning, funding and carrying out malaria research and control activities. We very much hope that these documents will raise awareness of the current status of knowledge of malaria, highlight identified needs and priorities, and play a major role in shaping future activities at international, regional and country levels.

Although the MIM Conference was a milestone in itself, we also regard it as part of a longer-term process of building African research capacity and bridging the gap between research and control. We hope this process is continuing beyond the Conference, with the

many contacts established and ideas generated, flourishing in the future and resulting in more cohesive continent-wide action against malaria. Some of the benefits and rewards should be clearly visible in a few years' time and we are confident that the next MIM Conference will see more African leaders giving keynote addresses and growing evidence of a closer working relationship between researchers and malaria control programmes. It is also our hope that reports from the public health arena will have started to bring news of successes in implementing plans to turn around the rising tide of malaria in Africa.

Catherine Davies **Brian Sharp**

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    Roll Back Malaria Project
    Special Programme for Research and Training in Tropical Diseases (TDR)

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THE MULTILATERAL INITIATIVE ON MALARIA

Origins and Objectives

The Multilateral Initiative on Malaria (MIM) is an international alliance of organisations and individuals that aims to maximise the impact of scientific research against malaria. Enhancing co-ordination and collaboration, mobilising resources, promoting capacity building in Africa, and encouraging research and control communities to engage in fruitful dialogues are major emphases of MIM.

The origins of MIM go back to meetings held in 1995 and 1996 between a number of organisations supporting research into diseases of the tropics. From these discussions emerged a recognition that ongoing activities were fragmented with different organisations independently supporting research activities at various locations across the developing world. There was agreement that a mechanism was required to orchestrate these individual activities into a more coherent approach, which would have a stronger and more sustainable impact. Malaria in Africa was selected as an important focus to develop a mechanism to promote greater co-ordination amongst the range of different players; and so the concept of the Multilateral Initiative on Malaria (MIM) came into being. The original overarching goal was defined as *"to strengthen and sustain through collaborative research and training, the capability of malaria endemic countries in African to carry out research required to develop and improve tools for malaria control"*.

A defining step in the evolution of MIM was a Congress convened in Dakar, Senegal in January 1997 where the scientific community was asked to identify the major research questions that must be answered in order for the problem of malaria to be addressed effectively (http://www.niaid.nih.gov/dmid/malafr/default.htm) (Bruno et al, 1997; Butler, 1997a). The meeting was successful in highlighting specific research priorities, as well as some broad recurring needs that cut across different subject areas. The recommendations arising from this meeting have played a crucial role in guiding the activities of MIM. Follow up meetings during 1997 in The Hague (Butler, 1997b,c; Gallagher, 1997) and London (Butler, 1997d; Williams, 1997) then defined more clearly the areas for concerted action and set out the strategies for addressing priorities. At the London meeting, the Wellcome Trust accepted the nomination to act as a co-ordinator of the activities of MIM for an initial period of twelve months. A series of key priorities were agreed upon at this meeting for action by MIM, one of which was to organise a pan-African malaria conference.

Key outcomes and future directions

MIM has been involved in a diverse range of activities since its establishment in 1997. Importantly, the Initiative has played a significant role in drawing additional funds into malaria research: overall funds committed to malaria research increased from an estimated US$85 million in 1995 (Anderson *et al*, 1996) to a figure of well over $100 million in 1999.

MIM is particularly concerned with promoting global co-ordination and collaboration in the malaria research community to address scientific needs and opportunities. To this end, it has facilitated links not only between scientists, but also between the funding organisations supporting them. MIM meetings, Newsletters and websites[1] have been important channels for enhancing communication amongst partners. Furthermore, the Malaria Foundation International has played a prominent role in raising awareness of the immense health and economic impacts of malaria.

There have also been unprecedented opportunities for interactions between scientists across Africa. The Dakar Conference in 1997 was a significant event in bringing together scientists from all regions of sub-Saharan Africa. Following the success of this meeting,

[1] http://mim.nih.gov ; http://www.malaria.org/mim or http://www.wellcome.ac.uk/mim

MIM made a commitment to establish a regular forum of this kind, leading to the first MIM African Malaria Conference in Durban.

MIM has also catalysed the establishment of formalised collaborations across Africa. Multicentre approaches can make a particular contribution by linking fragmented and isolated resources into networks which have the potential for much greater impact on malaria. Furthermore, single sites are not sufficient to obtain definitive answers in certain types of studies where large sample sizes are required, necessitating instead that standardised reagents and methodologies are applied at multiple sites. For example, a network linking five sites across Africa has been established to study severe malaria in children and particularly to evaluate novel treatments and develop new interventions.

To fulfil the need for standardised and well-characterised malaria research reagents identified in Dakar, a Malaria Research and Reference Reagent Repository, www.malaria.mr4.org/mr4pages/index.html, has been established with funding from NIAID. This facility will maintain and distribute reagents such as parasite strains, mosquitoes, genetic material (e.g. DNA probes) and antibodies.

The immense opportunities offered to African scientists by electronic communications technology and the internet have been recognised by MIM, and the US National Library for Medicine was nominated to lead an initiative in this area. Much improved connectivity has been achieved in Mali, and at two sites in Kenya, while plans for other sites in Africa are well advanced.

As part of its commitment towards building research expertise in Africa, MIM was responsible for the establishment of a new Task Force for Malaria Research Capability Strengthening in Africa, which is administered by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and is jointly funded from several different sources. This Task Force provides support for research training in association with large multicentre studies across Africa (www.who.int/tdr/workplan/mim.htm).

As another element of MIM's action towards strengthening research expertise in Africa, the Wellcome Trust carried out a review of current malaria research capacity in Africa and of research training opportunities for developing country scientists. The published report (Beattie P, Renshaw M and Davies C, 1999) (www.wellcome.ac.uk/en/1/biosfginttrpmimrep.html) presents unique data that provides evidence to inform strategic decisions on developing human and technical resources for malaria research in Africa.

These are just some of the activities in which MIM has been involved. Overall, MIM has helped to energise a new phase to improve approaches to international malaria research through creating new partnerships, and through providing a practical framework and point of reference to guide the activities of the international research community. The novel working relationships established between the major funders are also having an influence in improving co-ordination in the broader field of biomedical and health research in the tropics. In the future MIM will continue to tackle key priorities, as well as bottlenecks impeding progress. It is also committed to working with the WHO Roll Back Malaria Project to ensure smooth integration of malaria research and control activities.

The MIM African Malaria Conference in Durban marked the end of the Wellcome Trust's tenure of the MIM Secretariat function. It has been agreed that this role should rotate between partner organisations and the Fogarty International Center (FIC) of the US National Institutes of Health was nominated at the Durban Conference to become the new MIM co-ordinator. The FIC is committed to continuing the work begun by the Wellcome Trust in promoting capacity building and facilitating global co-ordination to ensure that research findings yield practical health benefits.

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MIM AFRICAN MALARIA CONFERENCE

Background and Rationale

The MIM Conference arose partly in response to the wish expressed by African scientists at MIM meetings for a regular forum in which they could meet to discuss progress, exchange scientific ideas and identify new directions. Prior to the establishment of MIM, there was a striking lack of collaboration and exchange across Africa in malaria research. Ineffective communication links across the continent, language divides and a dependence of the African science base on external funds tend to discourage bonds within Africa, and instead promote collaborations towards Europe and North America.

A MIM Meeting held in Dakar, Senegal in 1997 was a significant event leading to the organisation of the Durban Conference. This meeting was planned specifically to identify the key research questions that must be answered to make progress against malaria. To achieve this aim, it brought together key scientists from all parts of sub-Saharan Africa and a number of international scientists. In doing so, the meeting revealed the enormous potential benefits of greater interactions between sites across Africa and the significant lack of any opportunities for such interactions. MIM Partners' therefore agreed at a meeting in London in November 1997 that the organisation of a pan-African malaria conference should be a priority.

However, a major difficulty that had been identified as impeding progress against malaria, was the lack of adequate data for effective planning and implementation of control programmes. Hence, it was proposed that the MIM pan-African Conference, in addition to promoting communication and collaboration amongst scientists, should also be open to those involved in the practical aspects of malaria treatment and control. It was intended that encouraging dialogues between the research and control communities would assist in orientating research agendas to the needs of control programmes and facilitate uptake of research results into policy and practice. In this respect, the Conference built upon the successful model developed by the Southern African Malaria Conference, held in Maputo, Mozambique in 1997.

Objectives

The MIM African Malaria Conference was conceived to provide a forum to promote effective, unified action against malaria in Africa through high quality research in partnership with control programmes.

The Conference had a number of interrelated objectives:

1. To raise awareness of progress in malaria research, with a particular emphasis on studies in Africa.
2. To strengthen and facilitate key partnerships and communication links including:
   - Scientific collaborations across Africa and internationally
   - Regional and pan-African research and control networks
   - Links between the research and control communities
3. To identify research priorities for the future, including the data needs of malaria control programmes
4. To report on the progress of MIM activities

To meet its objectives, the MIM Conference was open to malaria scientists internationally, to control personnel and health professionals from throughout Africa, as well as to representatives of commercial companies and funding organisations internationally.

Format

The Conference agenda was structured across ten theme areas covering malaria research in its broadest sense and a designated co-ordinator was responsible for planning and running sessions in each of the theme areas.

1. Antimalarial drugs

2. **Communications & Connectivity in Africa**
3. **Economics of malaria**
4. **Ethics and research methodology**
5. **Health information systems**
6. **Malaria control and Roll Back Malaria**
7. **Malaria in preganancy**
8. **Management of severe malaria**
9. **Vaccines and immunology**
10. **Vector biology and control**

Daily plenary presentations by invited speakers highlighted key research results and opportunities, while parallel breakout sessions addressed the theme areas in greater depth. The breakout sessions were an opportunity for a broader range of speakers to present their work outside the plenary sessions. Brief presentations selected by session co-ordinators raised awareness of recent research advances and illustrated topical issues.

Time was reserved in between presentations to promote discussions amongst researchers, control programme personnel and health professionals. All delegates were encouraged to contribute their data and experiences to these discussions and to define:

- Research results with immediate implications for control programmes
- Constraints in current control activities that reveal data needs
- Short-, medium-, and long-term research priorities
- Ways of strengthening links between research and control
- Research capacity needs.

Although there was not sufficient time to consider research agendas comprehensively, progress was made towards identifying key research priorities within each of the theme areas. The highlights of the breakaway sessions were fed back into plenary presentations on a daily basis. Posters were another important mechanism for presenting additional research data and information on control programme activities. The last day of the Conference was devoted to a workshop on research training for African scientists, in keeping with MIM's capacity building objectives.

Opening and closing ceremonies

The Conference was opened by Dr Malegapuru Makgoba, President of the Medical Research Council of South Africa; Councillor Margaret Winter of Durban, and Dr Ben Ngubane, Minister of Arts, Culture, Science and Technology.

Short addresses were given by Dr Welile Shasa representing the African Regional Office of the World Health Organisation, Dr Michael Dexter the Director of the Wellcome Trust of the United Kingdom, Dr Maxime Schwartz the Director General of Institut Pasteur, France; Dr David Nabarro, the Manager for the Roll Back Malaria Project of the World Health Organisation; and Dr Harold Varmus the Director of the US National Institutes of Health. Dr Zweli Mkize the Minister of Health for Kwazulu-Natal Province gave the closing ceremony address.

Overview and outcomes

At the final count, delegates at the MIM African Malaria Conference numbered over 850 and came from 61 countries spanning all regions of sub-Saharan Africa, as well as collaborating countries outside Africa. More than 500 delegates came from Africa itself and approaching 100 representatives of the control community participated, including a strong presence from the WHO Regional Office for Africa (AFRO).

The scientific programme for the MIM Conference was planned by a Steering Committee that included pan-African representation. It was not intended to duplicate other meetings in Europe or North America, but instead had a particular emphasis on malaria research studies within Africa. All of the key African institutes engaged in malaria research were represented and the presentations closely reflected the breadth of studies ongoing in these institutes – having a particular bias towards clinical and applied studies. Key international scientists collaborating with African laboratories also made significant contributions, thus reinforcing scientific links between Africa and elsewhere.

Research progress and priorities

Presentations summarised the current status of our knowledge, but also looked to the future to urgent challenges and promises of new tools. While the *Plasmodium falciparum* genome project offers immense potential for new therapies in the long-term, reports from the drug and vaccine sessions on the immediate availability of new options were sobering. Results of the most recent trial of the SPf66 vaccine in Tanzania were revealed publicly for the first time, but disappointingly, no significant protection had been detected. A vaccine is likely to be at least ten years away and in the interim, other approaches to control malaria must be employed as effectively as possible. Prompt treatment of malaria remains a mainstay of many malaria control programmes, but the emergence of drug resistant parasites is a major concern requiring immediate action to protect our existing drugs as far as possible. The combination of standard antimalarials with artimisinin derivatives is an approach that offers important potential in delaying the spread of resistance and there were reports of studies underway to test this approach.

From the presentations and discussions emerged a range of subject-specific conclusions and priorities, as well as a number of needs that cut across all areas of activity and which clearly were not being addressed effectively by current approaches. One recurring theme was the need for detailed information on malaria in different localities. In view of the diversity of the disease across different areas, a standardised approach to controlling malaria across Africa is inappropriate. Local knowledge on transmission patterns, disease burden, vectors, patient populations, as well as on health systems and health treatment seeking behaviour is essential to plan and implement effective control programmes, but current information is sparse and additional trained personnel are needed to gather, analyse and interpret relevant information. The lack of expertise in the social sciences and health economics was recognised as a particular need. However, the expertise available probably is not being well-utilised due to sub-optimal linkages from economics and sociology to other areas of malaria research.

The need for clinical and operational research to evaluate potential treatment or control measures, and optimise efficient delivery of interventions was highlighted in many areas. However, the lack of incentives for well-qualified scientists to pursue more applied research in comparison with high-technology science was identified as being a fundamental problem working against these areas. Further thought is required to encourage more scientists into field and applied research and this may require a change in the common approaches to evaluation of research, which tend to place a strong emphasis on publications in high-impact journals.

Infrastructure for trials of drugs and vaccines requires long-term sustained investment, and advance planning is needed to ensure that appropriate infrastructure is in place in regions of varying endemicities. In the 'Severe Malaria' sessions there was a call for co-operation amongst scientists and funders to carry out large-scale studies to evaluate therapies that have sufficient power to provide definitive answers. The value of intensive, longitudinal household demographic surveillance to provide data to plan control activitis and to monitor progress was particularly emphasised and the need for further long-term (10-20 year) investment in this area ranked as an important priority within health information systems research.

One issue on which all of the breakout group discussions appeared to agree was that reinforcing and facilitating links between the research and control communities is essential for ensuring that research can have a major impact on improving health. The complexity of the process in moving from research to policy and practice was, however, fully acknowledged and the need to involve stakeholders in health policy from the earliest stages in the planning of research programmes was identified as essential in facilitating this process.

Capacity Building
In keeping with MIM's goal of strengthening research capacity in Africa, the Conference provided an opportunity for African scientists at all stages of their careers to present their work in talks or through posters for critical review in an international forum – a key step forward in the development of scientific skills. In all there were over 170 presentations in plenary and breakout sessions, with more than half of these presentations being given by African delegates from both the research and control communities. In addition, a research training workshop was held on the last day of the Conference and was highly appreciated by the 180 participants. There was a strong recommendation to promote such activities further, particularly as satellite activities of major scientific meetings.

Networking and planning activities
Not only did delegates tackle the main Conference agenda with enthusiasm, but they also participated in numerous additional workshops and satellite meetings – thus making the most of so many experts coinciding in one place. The numerous formal and informal dialogues that took place were clear evidence that although the language barriers between different parts of Africa, and between researchers, policy makers and implementors are considerable, they are not insurmountable

Importantly, representatives of the Southern African Malaria Initiative (SAMI) met to discuss progress towards strengthening regional cohesion. There were also meetings of a number of scientific networks operating across Africa including those to study severe malaria in African children (SMAC), malaria in pregnancy (PREMA) and highland malaria (HIMAL). The MIM/TDR Task Force on Malaria Research Capability Strengthening in Africa also convened after the Conference to review grant applications and to make decisions on new awards. Meetings of funders and participants in both the Multilateral Initiative on Malaria and Roll Back Malaria took place around the time of the Conference and were significant in progressing plans for these two major initiatives.

Another notable event that took place at the Conference was the first meeting of the African Malaria Society, following its inauguration in Italy. This Society was established with the aim of promoting interactions and excellence amongst malariologists in Africa. Professor Brian Greenwood of the London School of Hygiene and Tropical Medicine and former Director of the UK Medical Research Council Laboratories in the Gambia was honoured with the first Annual Award for major contributions to malaria research in Africa by a non-African scientist; while Dr Robert Howells received an award on behalf of the Wellcome Trust, for its role in co-ordinating the Multilateral Initiative on Malaria.

Poster Prizes
The MIM Conference attracted nearly 200 posters presenting the results of scientific research and the activities of malaria control programmes. The posters were reviewed and prizes awarded to three individuals:

- Dr Olumide Ogundahunsi, Department of Pharmacology and Therapeutics, Malaria Research Group, PRIMAT, Ibadan, Nigeria for his poster entitled 'Development of a community study site for the evaluation of antimalarial drugs, immunological studies and vaccines.'
- Mr Messay Gebremariam Fettene, Jimma Institute of Health Sciences, Ethiopia, and Department of Medical Entomology, South African Institute for Medical Research, Johannesburg, South Africa.
  'Identification of a new member of the *Anopheles gambiae* complex by polymerase chain reaction and single strand conformation polymorphism.'- M Fettene; M. Coetzee; RH Hunt and LL Koekmoer
- Ms Florence Soroses, Ministry of Health & Social Services, National Vector-Borne Disease Control Programme of Namibia for her poster on the Namibian malaria control programme.

Notes on these Proceedings
The format for the Conference, combining plenary overview talks and breakout group presentations and discussions was planned to give an opportunity to cover the broad

spectrum of research ongoing across the African continent. The transcripts of the plenary presentations and reports on the breakout sessions are an attempt to capture these valuable presentations and discussions. They have not been subject to extensive international peer review, but they represent the thoughts and views of the many scientists, from junior researchers through to eminent professors, who participated in the Conference.

The Conference was not designed to comprehensively consider and agree on priority research agendas. Nevertheless, the composition of the participants allowed substantial progress to be made towards identifying key needs and opportunities in each of the ten focus areas. Where possible, these priorities are brought out in the summary reports prepared by rapporteurs in collaboration with session co-ordinators and presenters. A feature of the Durban Conference, that differed from the Dakar MIM meeting in January 1997, was that the perspective on research priorities was influenced by the practical data needs of control programmes, through the participation of those involved in malaria control activities. The reports from Dakar and Durban therefore represent complementary volumes.

It is hoped that these Proceedings will play a role in raising awareness of the current status of malaria research activities and in influencing the future directions of malaria research towards yielding practical health benefits, both in a short time-scale and in the longer-term.

OVERVIEW OF MIM AND ROLL BACK MALARIA

Plenary Presentation

The Multilateral Initiative on Malaria from Daker to Durban and beyond.
Roy Anderson

MIM/TDR Task Force on Malaria Research Capability strengthening in Africa.
Ayoade Oduola

Introducing the Global Partnership to Roll Back Malaria.
David Nabarro

Breakout Sessions

Programme

1. Malaria Control and RBM I
2. Malaria Control and RBM II
3. Malaria Control and RBM III

PLENARY PRESENTATION

The Multilateral Initiative on Malaria: from Dakar to Durban and Beyond

Roy M Anderson, Wellcome Trust Centre for the Epidemiology of Infectious Disease, University of Oxford.

My task today, as assigned by the organisers, is to give a brief summary of what the donor agencies believe the **Multilateral Initiative on Malaria (MIM)** has achieved in the first few years of its operation. I would like to start with the general objectives of MIM, then talk through some of the specific developments that have taken place and explain some of the exciting research advances, before finally turning to what might be achieved in the coming few years.

I should say at the outset that the Wellcome Trust has very much enjoyed being part of this process and has been honoured to act as the nominated co-ordinator of MIM for this past year. Indeed the Trust has built up many wonderful collaborations and friendships with its partners throughout the world, both scientists and funding agencies.

The primary objective of MIM is "**to strengthen and sustain through collaborative research and training the capacity of malaria endemic countries in Africa to carry out research** ". This is a very laudable and important aim, and one in which I think significant progress has been made in the first two years. Particular emphases of MIM have been on promoting global communication and co-ordination, mobilising resources, building research capacity and then linking research to policy and practice. The aim was and is to encourage communication at many different levels: between scientists, medical research staff, and public health researchers, and importantly between funding agencies, to optimise the use of resources and avoid duplication of effort. A year or so into the life-span of MIM, the very exciting development from the World Health Organisation of '**Roll Back Malaria** ' was announced, and indeed a partnership between this new project and MIM represents a wonderful mechanism for taking forward the process of linking fundamental and applied research to policy and practice. Too often in the past there have been major research advances, but these have been slow to be translated into public health practice.

The meeting held in Dakar, Senegal in January 1997 was a very important event and discussions there centered on key research priorities and needs. Follow up meetings in the Hague and London then attempted to refine priorities for concerted action, and the Wellcome Trust became involved as a co-ordinator at the London meeting. The areas agreed upon for concerted action, by both scientists and funders, focused very particularly on addressing key research priorities and gaps, and exploiting scientific opportunities.

A number of recurring themes emerged from Dakar, which cut across different subject areas, and I would like to turn briefly to some of these. Clearly one of the most important issues identified was the isolation of scientists in Africa and the need for greater interaction and communication both across Africa and with the rest of the global scientific community. The issue of effective communication is an old theme, not specific to malaria, and it is a theme that is common across the biomedical and indeed the scientific and technological fields. A need for the standardisation of research methodologies and

reagents at different sites across Africa to enable comparison of results was also highlighted. In addition, there was much comment about the need for the creation of databases, for example, to track the evolution of drug resistance or assess if the incidence of malaria is declining or increasing in particular sites. These databases, of course, should be fully accessible to workers of all kinds, and particularly within the African continent, where longitudinal epidemiological data is required for planning disease control strategies. Another theme was the creation of networks, which can link together fragmented and isolated research resources to try to generate much greater impact. Multi-centre studies are often required to answer specific research questions, where single sites cannot achieve the sample sizes required to obtain definitive answers. Lastly the need for a repository of well-characterised research reagents was identified, such that scientists throughout the world could have access to a common stock for application in studies at different sites. These 'Dakar' themes have been the bedrock of what MIM has attempted to do in the last two years.

What are the key features of MIM? It is a loose alliance of organisations and individuals, including scientists, funding agencies, commercial organisations and those involved in the practical aspects of disease control. It is not a central funding body in itself, but it has nevertheless successfully drawn additional resources into malaria research, both through pre-existing schemes and through the establishment of new schemes. Of course, from its birth MIM has had teething troubles; and that is always to be expected with any ground breaking initiative. However, I have been very impressed, as an interested bystander, that those teething problems have been sorted out very quickly and indeed very warm friendships and collaborations have been developed between the partners. Perhaps one of MIM's most important roles has been as a focal point for communication between partners, and we see by the very occurrence of this Conference how well that focal point has served in bringing scientists together from all parts of Africa and all over the world. MIM has also provided a structured framework and point of reference to guide the activities of the international scientific community in a more co-ordinated manner. Indeed it has acted as a catalyst for action by scientists and funders, and I'm going to turn specifically to some examples of that in a minute. MIM is in no way attempting to direct scientists, but is trying to respond to priorities that they themselves have identified and to encourage them in their activities. Where possible, MIM aims to add value to efforts to address specific problems, such as drug resistance, by encouraging synergistic activities.

Who are the partner organisations in MIM? There are quite a number and they encompass a range of different types of organisations, each with their individual objectives and remits. It has, however, been extremely encouraging to see how these diverse organisations have worked together under the MIM umbrella. Of course the World Health Organisation and the programme of Roll Back Malaria will play an increasingly important role in coordinating partners within the broader malaria community.

On the communications and publicity aspects of MIM, there have been a number of different approaches adopted. Publicity for MIM, and the general significance of the social and economic impact of malaria in the world today, has been handled very well by the Malaria Foundation International. Meetings, web site information and the MIM Newsletter have also contributed to promoting communication between partners. The communications side is one where our timing was right in terms of opportunities offered by new technology: such technology has changed out of all recognition in the past five

years. Meetings and workshops, where we have personal interactions and informal discussions, are of course extremely important, but today a great deal can be achieved via electronic mail, and of course the world wide web is an increasingly important communicator of scientific and other information.

I want to dwell on electronic communications a little further because the US National Library of Medicine, which is part of the US National Institutes of Health, has been leading an effort to improve the access of African scientists to electronic communication facilities. I think all of our lives have been changed in the last few years by the way we use e-mail to facilitate friendly chat and scientific correspondence, but most importantly to circulate documents and scientific papers plus analyses of particular results or events. This transformation has had a dramatic impact on the international scientific community and is beginning to have an extremely important impact in Africa itself. The world wide web is an extremely important educational tool even at the cutting edge of research. For example the accessibility of databases via this route greatly facilitates international research. The database of the falciparum genome project, or perhaps databases linking global patterns of rainfall to the occurrence of mosquito vectors of malaria are good examples in the malaria research field. MIM of course has not been responsible for the technology, but it has been responsible, via its collaborators, in providing much greater access. An important start has been made in the context of providing greater access to African scientists to the web and electronic communication, but as many of you in the room will know, much remains to be done in this area. I am certain that this one single aspect, namely effective communication, can do more than most other things to promote taking malaria research findings into public health practice, and equally encouraging the growth of biomedical research in Africa.

Regarding support for malaria research, the figure in 1994/95 was about $85 million internationally, a very small amount in relation to the global burden of morbidity and mortality imposed by the disease. There are as yet no up-to-date figures for this year, but it is clear that there has been a considerable enhancement by a variety of agencies. The estimated commitment is currently well over $100 million per annum. Indeed there are a variety of encouraging trends and further increases may soon be announced. Again, MIM has been a part of that process. Some of these things would have taken place of course without MIM, but the Initiative has helped to augment and stimulate certain agencies to contribute more to malaria research.

In terms of promoting global collaborations, MIM has provided unprecedented opportunities for interactions amongst African scientists, and there has also been good progress in promoting communication between Africa and the rest of the global research community. Similarly, there has been a remarkable level of communication amongst funding agencies. There is room for further progress, however, in promoting collaborations and communications between industry and the other parts of the malaria community. In taking this initiative forward in the coming years, I do hope that those of you who are industrial representatives here, can persuade your boards and your senior scientists to play a larger role in the activities of MIM. You are a most important contributor to taking research into practice via the development and promotion of products, whether these be impregnated bednets or new drugs, and indeed hopefully in the longer term, vaccines. There is also scope for further strengthening of links between the biomedical research and public health control communities; an area where the current

Conference aims to make a significant contribution. It is often the case that new findings on the treatment of severe malaria or on the relative effectiveness of different control options take a long time to get from the pages of major scientific and medical journals to the community suffering from endemic disease.

Multi-centre studies and networks, as I mentioned earlier, are important for maximising the impact of activities across Africa and a whole variety of them have been established or strengthened since the creation of MIM. Again, MIM has not necessarily been responsible for all of these, but it has added to their impetus and in very real ways contributed to financial support for a variety of these. One example is the Severe Malaria in African Children Network, which links five sites across Africa for the evaluation of novel malaria treatments and for the development of new interventions. Another example is the East African Network for Monitoring Antimalarial Treatment Efficacy (EANMAT) which was established for standardised assessment of drug resistance at different locations in the East African region, bringing together both scientists and ministry of health representatives. The establishment of the MIM/TDR[1] Task Force for Malaria Research Capability Strengthening in Africa has been a significant development in providing a mechanism to facilitate linkages across Africa and to promote research training and capacity building. The Mapping Malaria Risk in Africa (MARA) project is one important programme that has received funding via this scheme.

I want to now turn briefly to some specific research activities, an area in which I personally feel much more comfortable with. Again, MIM has not been the key component of the research process, as it were, but it has been a very important supporter of a variety of activities. In the area of immunology and vaccine development, support has been provided by NIAID for studies of human immune response to malaria in endemic regions, and the NIAID malaria vaccine development unit has also been expanded for activities such as the production and evaluation of clinical grade immunogens. In the European context, a Malaria Vaccine Research and Development Network has been supported by the European Commission; as has a very important centre, the biomedical primate research centre, which of course we all dearly hope will be the site for future studies on potential vaccines. Importantly, in direct response to the need identified in Dakar, NIAID has established a repository of well-characterised malaria research reagents, such as parasite strains and monoclonal antibodies.

If we look back over the past few years, the malaria research community has been very active indeed. Malaria publications have appeared in the leading scientific journals, such as Science and Nature and in the leading medical journals, such as the New England Journal of Medicine and the Lancet and so forth. And so the community itself has had a very high presence, and it is without doubt an extremely exciting time research wise. There are extraordinary opportunities at the moment and what is required is more individuals contributing to this from African and other developing countries.

It is always dangerous to choose a set of research fields to mention specifically, and indeed I cannot do justice in a very short period of time to the whole range of exciting advances that have occurred recently. I do, however, want to mention a few areas, and you will hear

[1] TDR: UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases

about many others in the specialist meetings within this Conference. The *falciparum* genome project is of course undoubtedly an extraordinary opportunity and one that is progressing extremely well, and I will turn to the details of that in a minute. There have also been very important advances in immunology and pathogenesis, and particularly in our understanding of the causes of severe malaria. Quite surprisingly, there has been significant progress in our epidemiological understanding of malaria disease, even though many of us would have thought malaria epidemiology was a subject that had been worked to death. Particular progress has come from the results of very long-term observation of communities, and important information has been generated on the relationship between exposure to malaria and disease severity; a key factor in interpreting the likely success of different interventions. Another important development is in the process of evaluating intervention studies. We now have a range of methodologies and approaches for looking at cost benefit analysis in a much more rigorous and quantitative manner, where economics, quantitative tools and epidemiology merge together to try to assess what is the most cost-effective intervention in a particular setting.

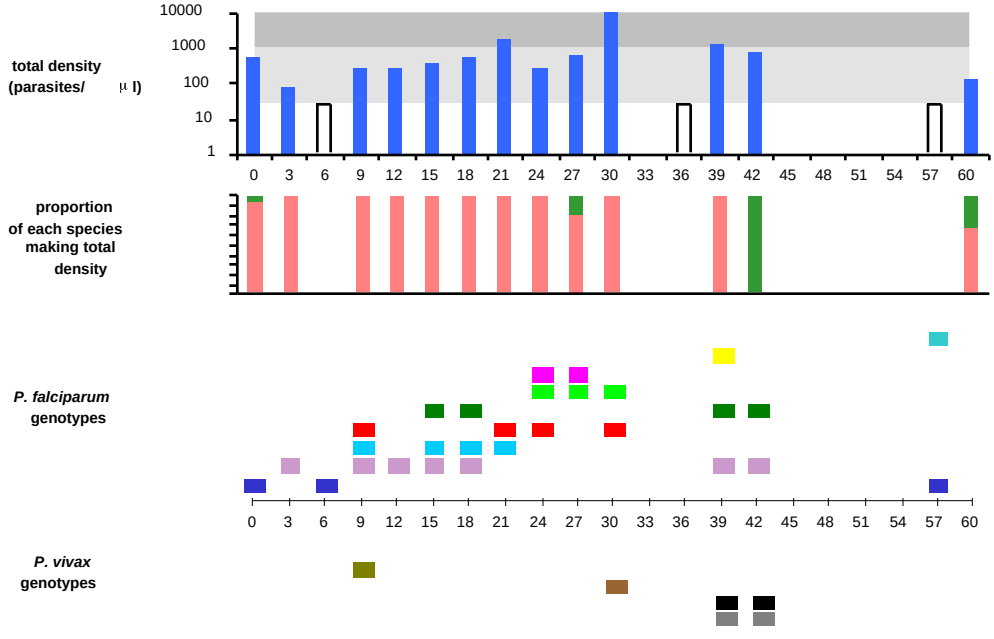
An important clinical development has been the drive to use combination therapy in the treatment of malaria, which was brought to the attention of the broader malaria community at a MIM meeting held in May 1998, and has been very much supported by MIM. To many in the broader infectious disease community, it is somewhat of a surprise that it has taken malaria researchers so long to get to this stage, given the extraordinary successes of combination therapies in the treatment of tuberculosis and indeed more recently, of HIV. One of the key problems in all of these cases is the evolution of the infectious organism under intense selective pressure, and hence the need to vary the selective pressure, for example through the use of drug combinations. Very exciting developments have taken place over the past two years in this field, in which Professor Nick White has been very influential.

I am going to choose just one or two research advances, which are very important for a whole variety of reasons. They are, however, primarily selected because of my familiarity with them, and there are many others that I am less familiar with that are of undoubted equal importance. I would like to mention a study carried out by Karen Day's group, which is not in Africa, but in Papua New Guinea. Particularly important features of this study are its extremely long-term nature and its interdisciplinary character, involving molecular biology, clinical studies and field epidemiology. The research involved longitudinal study of individuals to assess their exposure to parasites over a long period of time, and this is a type of study that the Pasteur Institute in France has also actively supported in Western Africa. Understanding exposure of the immune system to different antigens is crucial to vaccine development in the future. We have had some disappointments in vaccine development in recent years and many believe that this is in part due to our lack of understanding of the complex genetic structure of populations of malaria parasites. If we take some illustrative results from a single patient, a male child aged 10 years, in the study by Marion Bruce, Karen Day and others, the slide (Figure 1) shows total parasite density at the top over time, followed by the proportion of infections that are *Plasmodium falciparum and P. vivax* . Most importantly, the lower graph records temporal changes in the patient of the densities of different *P. falciparum* genotypes as defined by two locuses of MSP2. These results demonstrate that individual children are repeatedly exposed to a heterogeneous parasite population as they age. One of the problems in developing vaccines, therefore, is that the parasite population is not static, it is constantly changing in

its genetic and most particularly its antigenic composition. Indeed, because of recombination, which occurs at moderate frequencies in high intensity transmission areas, developing a vaccine for malaria (or HIV), is an issue of trying to keep ahead of parasite evolution. One strategy, is to seek conserved regions of the genome which elicit protective immune responses. This is not an easy task, however, since the parasite via evolution and selection has acquired mechanisms for generating antigenic diversity in those parts of the genome which are presented to the human immune system, and this is a very common strategy among successful infectious agents. The task of understanding parasite evolution and the constantly changing genetic structure of malarial parasite populations is very challenging and will involve molecular epidemiological studies on a scale many orders of magnitude larger that past studies.

Figure 1 - *P. falciparum* genotyping: Size and sequence polymorphism at the *Msp2* locus
(Bruce *et al*, 1999)

Child 31: Male, age 10

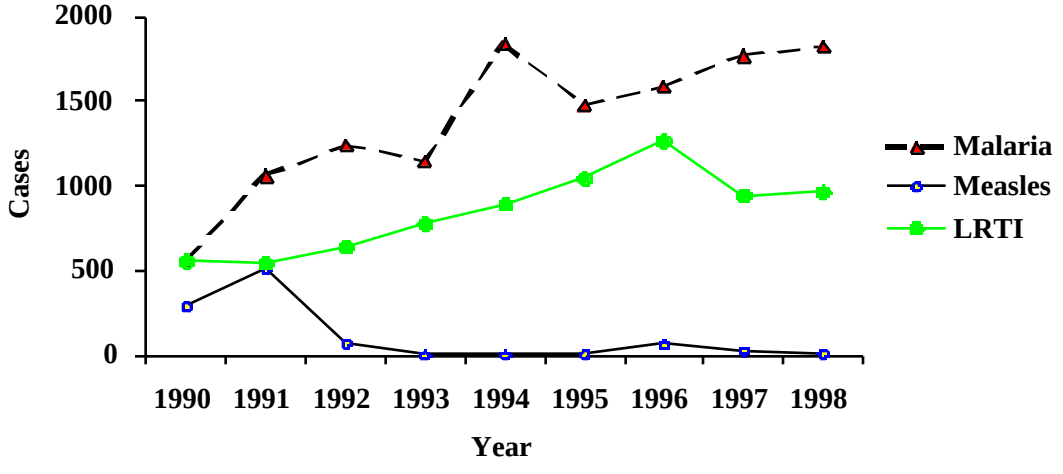


I now want to move on to mention the cross-sectional and longitudinal studies of Kevin Marsh and Bob Snow in the Kilifi area in Kenya. A particular feature of these studies, which I feel is extremely important, is the detailed demographic study of villages over a long period of time. You cannot hope to interpret the epidemiology of malaria unless you understand something of the demography and movements of people. This study combines a whole variety of different skills: clinical, demographic, epidemiological, vector control, and indeed more recently, economic approaches. It is always important to bear in mind that the problem of malaria control is not a static entity. The world population this year is due to exceed the six billion mark and virtually all of that population growth is in the less developed regions of the world. If we look at its distribution between Africa and other regions, the dominant part of the population growth will occur in India first, China second, and Southeast Asia third. Africa, particularly Nigeria as an example, will also make a very significant contribution to net global population growth. So our problem with any infectious agent, whether this be dengue, measles, malaria or whatever, is that the intensity

of transmission is often intimately linked with the density of the human species. The problem of increased population size is going to add to our difficulties in controlling malaria and we therefore have to understand the demographic aspects of the disease, as well increasing our understanding of epidemiology and the treatment of disease.

Records from the Kilifi district hospital (displayed in Figure 2) reveal changes over time in three infectious diseases: malaria, measles and lower respiratory tract infections; the latter of course representing a mixture of infectious agents. The impact of measles immunisation is evident in 1991, but there is a steady rise in respiratory diseases and malaria. This slide illustrates the value of longitudinal studies in close cooperation with African partners and funding organisations, which provide a very important long-term infrastructure for the investigation of both clinical and epidemiological issues.

Figure 2: Malaria, LRTI and Measles patients admitted to Kilifi District Hospital
(Marsh *et al*, 1998)



It might be argued that the rise in the number of cases is due to enhanced reporting or increased attendance at hospital, resulting from the presence of the malaria research centre in the region. The importance of quality longitudinal data, however, is that it enables you to pose very specific scientific questions about epidemiology and the impact of control measures. For example, the association between the incidence of malaria cases and rainfall can be tested. The use of technology such as satellite remote sensing can be used to analyze the association between physical and climatic factors and the spatial distribution of disease. This approach has been used extremely successfully in the field of trypanosomiasis to map tsetse fly distributions and associated vegetation and climatic variables, and is beginning to be used extensively in the malaria field. The application of new technologies to examine associations between disease incidence, climatic conditions and geographical information will, I believe, play an important role in future surveillance and epidemiological investigation.

Of course the practical end of malaria research is trying to make an impact on community health. The work of Vicky Marsh and Bob Snow provides one particular example of an

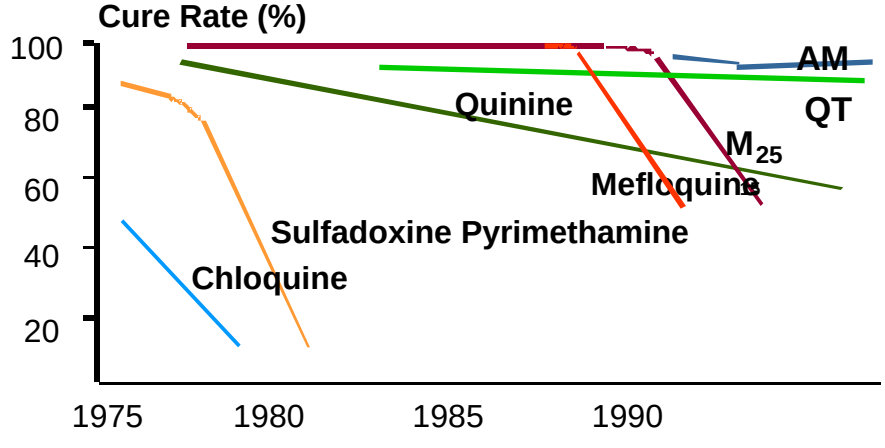
attempt to improve on the early treatment of malaria through education of shopkeepers. Lateral thinking was involved here in trying to decide how best you get research understanding into practice: shopkeepers who may potentially distribute anti-malarial tablets represent a wonderful target for education. Much more of this sort of innovative research is needed.

Emerging resistance to current antimalarial drugs remains one of our greatest problems and a significant component of this Conference will be devoted to this issue. A MIM meeting on this subject was held in May 1998 and perhaps one of the most important outcomes was a commitment from a number of agencies to support safety and efficacy studies on combinations of artemisinin derivatives with other antimalarial drugs. This work is progressing rapidly, and it represents a very important development in trying to use a scientific approach to manage the evolution of drug resistance; and MIM has been important in this process.

The focus of MIM has been on Africa, where malaria has its greatest impact, but it is important to recognise that malaria is also a significant problem in Southeast Asia, India and indeed South America. Hence, I believe that in the future, MIM should perhaps consider extending its activities to these other regions of the world with acute malarial problems. The Wellcome Trust has for a long time supported studies on the evolution of drug resistance in Southeast Asia directed by Nick White in partnership with staff at Mahidol Univeristy in Bangkok. This is a further example of long term commitment to research in partnership with the government of a malaria endemic country. It has provided unique information on the development of drug resistance. The cure rate for patients attending at a hospital in Thailand was studied for various drugs over a period of time (Figure 3).

Figure 3: Resistance in Thailand 1976 – 1998

(White *et al*, 1998)

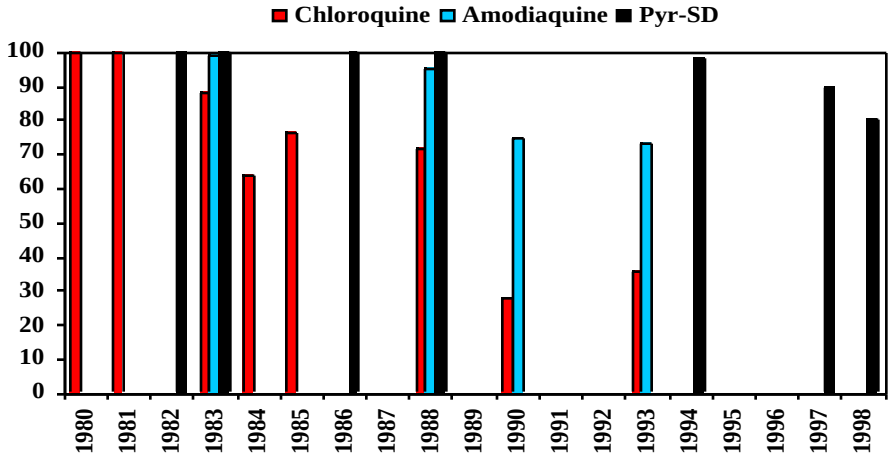


Chloroquine was the first to exhibit the rapid evolution of resistance, followed even more rapidly by sulphadoxine-pyrimethamine. These sorts of long term longitudinal studies provide a lot of information about the mechanisms of evolution of resistance. Another example from Bill Watkins and colleagues studies in Nairobi showing a dramatic fall in sensitivity to chloroquine, but again the important feature is the longitudinal nature of the study (Figure 4). Longitudinal data based on good sampling and reliable tests is an important beginning in mapping the evolution and persistence of drug resistance.

However, to better understand the relationship between the frequency of resistance and the intensity of the selective pressure (i.e. volume of drug consumption) we also need to encourage governments to put in place surveillance of drug consumption patterns and how these change over time and in different locations.

Figure 4: Antimalarial drug sensitivity at the Kenyan coast 1980 – 1998

Watkins *et al,* 1998



We have to go further than this though. Technology offers extraordinary opportunities here: scientific advances have provided us with molecular probes, such as DNA probes, to type very quickly in laboratory or field settings, the presence and frequency of resistant organisms. I would, however, make a particular appeal to the clinical and drug resistance community, that you cannot truly understand these patterns if you only measure one part of the equation, namely, the frequency of resistance in patients. Standard evolutionary theory tells us that the speed of the evolution of resistance is a function not only of the mechanism by which resistance is conferred, but also of the intensity of the selective pressure, or the level of drug use. We know very well from the antibiotics field, that if you can record and quantify drug use it can give you important insights into whether there is a critical level of use where you switch into high levels of resistance frequency and so forth. So in the malaria field we need to move forward to understand patterns of drug use in a quantitative, longitudinal sense.

Studies of the prevalence of malaria infection in relation to the intensity of transmission has recently revealed some important findings. As we move into more intensive intervention studies, whether by bednets or other means, we have to understand the relationship of severe disease to transmission intensity in much finer focus. Work by Snow and colleagues has generated some significant data on the age-specific incidence of serious disease. In view of the focus of disease in the younger age groups, it is evident that any intervention will shift this pattern of age dependent disease. Generally in infectious disease epidemiology, reducing the intensity of transmission raises the average age at infection. Quite subtle quantitative calculations need to be done on the intensity of intervention required not to shift this serious burden of morbidity into older age classes, but instead to reduce it significantly. The progress in our understanding of the relationship between serious disease and exposure has been important, and one that MIM has encouraged.

Finally, the malaria genome mapping and sequencing project is a wonderful scientific advance, which is progressing extremely well at present. For maximal efficiency, the 14 falciparum chromosomes have been divided up between sequencing centres in the United

Kingdom and the USA, supported by various funding agencies. The project is an excellent example of a collaborative, co-ordinated approach by both scientists and funders to achieve a large-scale scientific objective. There has been astonishing progress: Chromosome 2 is already finished, Chromosome 3 is almost complete, and there is closure on Chromosomes 1 and 4. The project is likely to be completed ahead of schedule. It really does offer the most extraordinary opportunity for understanding a whole variety of key scientific issues. Completion of sequencing is of course only the beginning, and there are further important stages to exploit this information. Firstly, understanding what genes do and whether they offer sensible targets to modify or block the specific gene product to the detriment of the parasite; and then secondly, assessing malaria diversity. Genetic diversity is key to understanding a wide variety of problems including vaccine development, drug resistance and pathogenicity. The genome projects, undoubtedly will move more into diversity studies in the coming years, as most of the important human pathogens are sequenced.

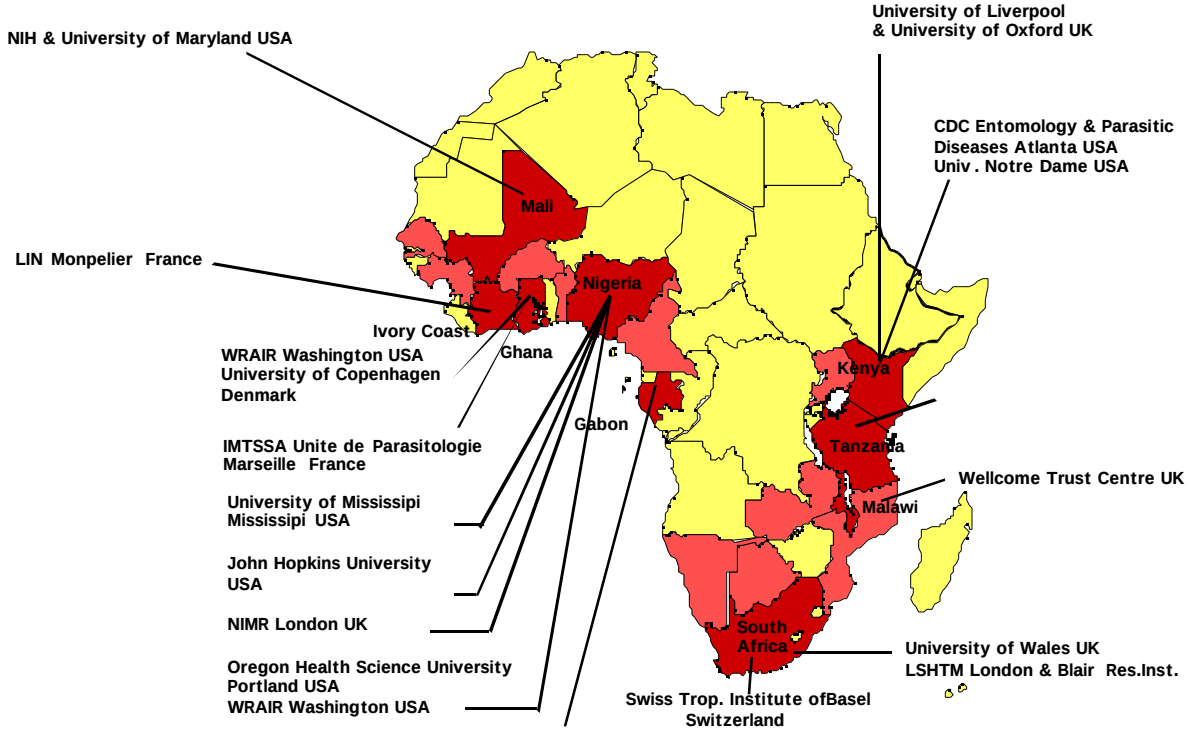
Finally, I would like to refer to the current MIM Conference. There is an exciting programme in store, and it is an exciting time to be a biomedical scientist. There are many scientific opportunities, but our real challenge, which will be addressed by David Nabarro, is to turn these exciting opportunities into practice, and to make a difference in the fight against disease. That is something that we have failed to do in the past in a number of infectious disease fields, HIV being a very dramatic example, and we must not fail against malaria.

To end on the point I started with, the Wellcome Trust thanks the community for its tremendous support and all our partners, who we have greatly enjoyed working with. The role of MIM co-ordinator will soon be rotating onto another agency and we wish our successor great success in taking the Initiative forward in the coming year. My own impression of MIM is that it has made a good start, there have been some very specific things that have been achieved by MIM, but there is a lot of hard work to do as yet. Promoting effective communication is of very particular importance.

The MIM/TDR Task Force on Malaria Research Capability Strengthening in Africa

Ayoade MJ. Oduola, Postgraduate Institute for Medical Research and Training, College of Medicine, University of Ibadan, Ibadan, Nigeria

It is a honor to present an overview on the Multilateral Initiative on Malaria in Africa (MIM/TDR) Task Force for Malaria Research Capability Strengthening in Africa at this historical Conference. I am sure that everyone here has seen the lists of the projects that have been funded through this initiative. What I would like to do in the time allotted is to talk about the rationale behind this effort to build capacity for malaria research and control in Africa, and to highlight the philosophy that serves as the driving force for those who are supporting the initiative. I hope that the principle behind the initiative will become clear and receive the necessary support from African scientists, and at the same time provide a strong rationale for the funding agencies and the international community to continue to provide financial support and expertise for the initiative.



We have listened in the past thirty minutes to all the achievements in science and technology that have accrued over the last ten years and the results of the efforts by MIM in promoting utilization of some of the achievement in efforts against malaria in Africa. The potential contributions of impregnated bednets, the new anti-malarial drugs that are in the field, and the genome project that promises advances in terms of new drugs and vaccine developments have been presented with great hope for control of malaria.

The question that comes to mind after the presentations is, if all these facilities and advancements are available, why do we need capacity for malaria research in Africa and why are we still subjected to the problem of one million children dying from malaria in Africa? The current situation in Africa is a simple one: all of these facilities require human resources, well-trained scientists, investigators and control managers who understand how to adapt and implement these facilities for controlling malaria. If you have insecticide

treated bednets available in Africa today, would those involved in malaria control at the ministry of health identify the appropriate population and community where it should be implemented for maximum benefit? Antimalarial drugs derived from the Chinese herb Artimisinin are now available and studies by Professor Nick White and the other investigators have shown that these drugs should not be used alone because of the danger of selection and dissemination of resistant strains of the malaria parasites. How many of our investigators in Africa and those charged with the policy making or implementing control programmes are aware of the need to use this drug in combination with other antimalarial drugs in order to prolong clinical life of this valuable drug?

These underscore the lack of critical mass of investigators, control managers and infrastructures that are necessary to monitor post deployment of these instruments, so that we do not end up with a DDT story, which will be demonstrated by rapid generation of resistance to new anti-malarial drugs and insecticides. We are all quite aware of the unfortunate financial situations of our governments in Africa. There is no single government beside the Southern African corner that has sufficient funding allocation to malarial control programmes in Africa. Funding for most research activities come from the Northern partners; often through collaborations between Northern investigators and resident African investigators, who are few. In order to better utilize tools against malaria there is a need for access to technologies that are often unavailable in Africa. However, the extent of interaction between investigators in Africa and those of the North is often limited, with the exception of those who trained in Northern facilities and retain their umbilical cord with the supervisors. More importantly, African countries lack opportunities for collaboration with each other. For example, communication between Nigeria and Cameroon is non-existent and discussions between a researcher in Southern Nigeria and someone in Mali requires 24 hours of travel to Bamako in order to plan or implement anything that would be productive.

These are major reasons why MIM focuses on seeking solutions that would be useful in terms of making better utilisation of the new technologies available to Africa. The philosophy is to develop a unique strategy that takes into consideration existing facilities and competence that is currently available in Africa, with the aim to enhance and efficiently utilise these limited resources and the support of the international community. It was also noted that implementation of this unique strategy must be based on a philosophy that every stake holder can appreciate and support. There is no looking for new funding for new structures. Instead we need to build upon existing strengths to promote productive utilization of the technologies that can be transferred and adapted from the developed countries. This requires using the strengths of the ministries of health, and of government universities that are responsible for training training young scientists, and building on the interests, support and expertise of Northern partners to transfer technology to Africa in promoting effective control of this devastating disease.

In order to accomplish this objectives, the Multilateral Initiative on Malaria in Africa (MIM) charged the UNDP/World Bank/World health organization Special programme on tropical Diseases Research and Training (TDR) with the challenge of bringing together stake holders with interest in supporting capacity building research and control of malaria in Africa. TDR as a Special Programme at WHO spent the last 25 years on training and research capacity building in tropical diseases research all over the world. This training programme has had many successes. A significant number of those attending this

Conference have benefited from TDR programmes. In order to accomplish this objective, TDR focused on putting together a Task Force of international experts with a unique approach on the composition of the members. The MIM/TDR Task Force was designed to be made up of at least 50% African scientists. The question that one may ask is why 50% African scientists? Well, we have the experts and technological know-how in the North, but knowledge of the socio-cultural situation that is necessary for successful implementation of this expertise in Africa communities, resides in the African population. The African experts that are aware of the problems often do not have the opportunity to access and interact with experts of the North to promote effective utilisation of tools. It is in this respect that the composition of the Task Force becomes an important factor in the success of the initiative.

Let us for example examine an anecdotal situation with a study in India that aimed to assess the effects of introducing impregnated bednets. The community that was chosen for the study was a small village, and after studies in the area, it was observed that there was apparently no effect - until a member of the ministry of health pointed out to the researchers that most of the population worked at night and therefore did not benefit from the bednets. These are situations that you also find in Africa communities that may not be apparent to investigators. Introduction of artemether or artesunate suppositories in Africa will require an understanding of the cultural predilection not to accept administration of drugs via a route that is generally taboo in African communities. To convince a mother that drugs that are usually administered by mouth or by injection now have to go through the opposite end of the child requires contributions on detailed understanding of the sociocultural factors which can be provided by those working within African communities.

This underscores the rationale for ensuring Africa's involvement in the MIM/TDR Task Force. The Task Force at its inception insisted that its programme must be different, and should not be equivalent to research projects funded through other international funding programmes. How do you obtain such uniqueness in an environment that is saturated with many success stories and with brilliant programmes that have been well-crafted by different agencies? This led to a search and much discussion on how to implement the unique strategy criteria outlined by the group.

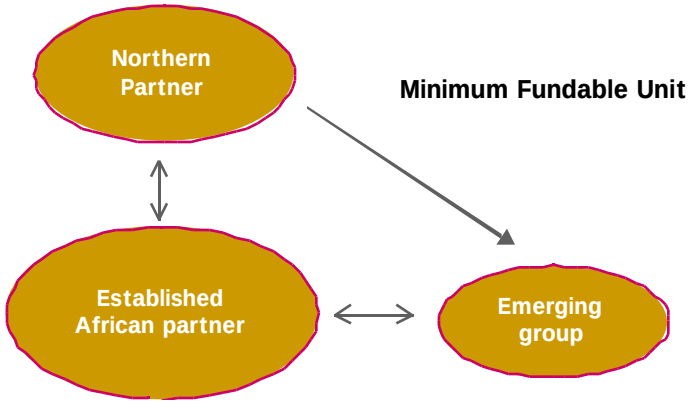
The first of the criteria that was agreed upon is to ensure that there is a congregation before building a cathedral. In the past, laboratories were often built before training investigators to utilize the facilities. The development of human resources must precede provision of infrastructure, and infrastructure must meet the needs and conditions available in Africa. Later, the human resources built up in one location can be used to enhance the development of other institutions. For example, training in Mali for investigators from the Benin Republic and opportunities for young scientists from Congo to train at the MRC in South Africa, and similarly for students the Niger Republic to undertake PhD degree studies at Ibadan, Nigeria represent effective utilization of the limited resources in Africa.. Availability of infrastructure and a critical mass of investigators at each institution can thus be used to promote group linkages. Promotion of interactions between research or control groups in Somalia, Ethiopia and Kenya, with the opportunity for investigators and control managers to discuss indiginous problems and provide indiginous data necessary for policy making in this context represents a prerequisite for a successful malaria control initiative in Africa.

It is apparent from the programme of lectures and activities scheduled for this Conference that the list of African investigators participating as leaders of research or control groups is short. It is not that they do not exist, but they are few and far between. To address this, the programme proposed by the MIM/TDR Task Force provides the opportunity for training African leaders. It is not enough to train workers to collect data or samples for malaria research or control. We need opportunities for African investigators to be in positions to determine the priority and focus for research and control in their immediate communities. There is a need for opportunities to train programme managers who can translate the findings of of both local and international research and inform decision makers of the potential value of utilising indiginous data in evidence based policy making and implementation.

Today there is to a large extent a blanket approach in terms of management of malaria in Africa. A single drug recommendation is used across the continent and a switch from the first choice of anti-malarial drug is based *a priori* on factors that are irrelevant to the parasite population and irrelevant to the effectiveness of the drug in specific patient populations or demography of the community. Instead, it focuses more on the ability to pay, or if the budget of a country is sufficient to sustain the change. A critical number of trained local leadership and expertise in science and control, provides valuable opportunity for appropiate determination and policy choices based on unique and peculiar factors in the population without extrapolating directives for Nigeria from data obtained in Ifakara. These indigenous experts can then advise their governments on the procedures that should be involved in policy making, based on uniqueness and peculiarity of the community. In addition, it is clear that a well trained investigator in Nigeria can co-operate and collaborate with investigators from Oxford and London exchanging views on local factors that can enhance the potential successes and drawbacks of applying new technology developed in their laboratories. Today a large number of models that have been applied for malaria control and research in most of the African countries are based on wholesale importation without relevance to what is available and what should be considered in the communities, and this has led to limited success. With this in mind, the MIM/TDR Task Force decided that it had to look for uniqueness in its programme, and should ensure that the underlying philosophy must be made known to all those participating.

What are the characteristics of the programme that the Task Force came up with that differentiates it from the current standard of practice in grants and programmes? The minimum fundable unit is one unique aspect. The Task Force proposed that each project should involve at least three entities, consisting of a non-African partner from any place in the world. So far, the non-African partners are mostly from Europe and the United States of America, but we are also hoping for involvement of partners from Southeast Asia, South America and Australia. The unit must also include an African institution that has enough scientists or control experts trained at one level or the other, but which does not have the infrastructure or equipment essential for promoting the excellence that is desired for successful contributions to malaria control or research. Finally, the unit must include an emerging African institution that has only a few scientists or control experts, but is interested in contributing to the effort against malaria by developing a critical mass. The hope is that the non-African partner will contribute in efforts to transfer the needed technology and continue to contribute to training of the African partners at the established institution and at the emerging institution. The Task Force provides funding for

the infrastructure and equipment needed by the established institution, so that it can effectively utilize and incorporate the new technology transferred from the North.



What else is unique? The principal investigator representing the three partner institutions must be an African working and resident in Africa, because leadership can only be learnt through practice. The intention is that leadership can be acquired by practicing with a Northern partner who has experience in such leadership. The principal investigator in effect is not only leading a group, but is also learning how to run projects, how to successfully execute programmes and acquire knowledge of how to source funds to maintain a programme. In addition to this, for the first time in the history of science and research in African, TDR and WHO were permitted to pay salary supplements to the investigators. Why is this important? The economic disadvantages in Africa results in a major problem of 'brain drain'. A large percentage of those trained in Europe and the USA remain there or migrate to the middle east, because they cannot get sufficient financial remuneration in Africa to maintain their family and contribute meaningfully to the research or control process.

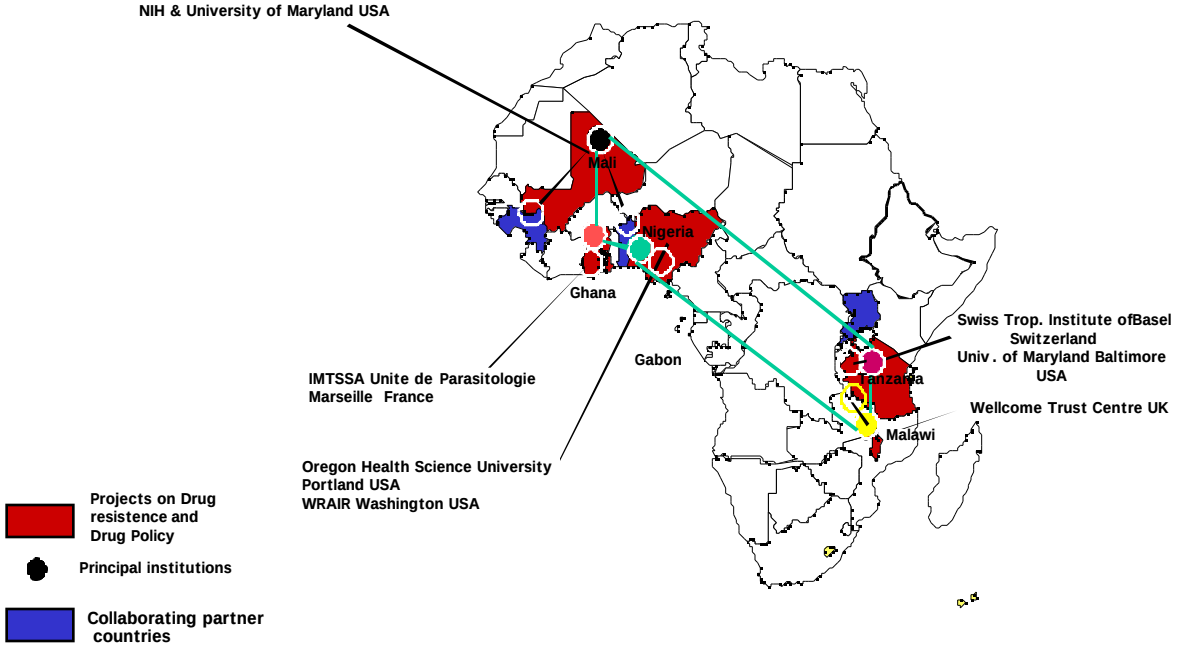
Of great importance, is the emphasis laid on the need for the MIM/TDR programme to be science driven – funds should not be provided just to buy science equipment or support PhD training. In order to achieve this, the Task Force identified a number of research priorities, including anti-malarial drug policies and drug resistance, epidemiology, pathogenesis, vector studies and health systems research including social sciences which we know are essential in utilising new drugs and other interventions for a successful malaria control programme. The location of training for African scientists was also agreed upon: this training must occur primarily in a research environment in Africa, but there is also the opportunity for 3-9 months training overseas. The rationale for stipulation on location of training was predicated on a need for African investigators to keep abreast of local situation and focus their programme of training on relevant problems in Africa. This permits acquisition of knowledge and new expertise without loosing "touch" with the reality of the malaria problem in the community. It also provides the advantages of developing the African institutions while training the new generation of investigators.

The Task Force will support relevant research projects or programmes covering, but not limited to, the following priority areas, including cross-cutting innovative approaches.

- **Antimalarial drug policy and chemotherapy** - development of strategies for rapid mapping of drug resistance; innovative approaches for preventing, retarding and reversing drug resistance; definition of criteria for replacing first

line drugs; identification, selection and evaluation of alternative first and second line chemotherapies (including combinations); and development of new drugs based on phytomedicine.

- **Epidemiology -** the use of new technologies to identify parasite diversity in various settings; the relationship of parasite diversity to immune responses and host resistance; analysis of the relationship between transmission, infection, disease patterns and deaths in order to design effective intervention strategies; development of methodologies to measure the impact of interventions including drugs, bednets and vaccines on disease and parasite diversity; development of new approaches to testing vaccines and drugs in different populations including adults; and development of simple and rapid epidemiology mapping methods.
- **Pathogenesis** - studies on parasite-vector-host factors (including immune responses) iinvolved in severe disease and malaria in pregnancy, with the aim of developing and promoting improved preventive and case-management strategies.
- **Vector studies -** application of newly developed molecular tools for studies on vector biology, feeding behaviour, vectorial capacity, insecticide resistance and population genetics with the aim of identifying and developing effective strategies for vector control in focal, low and high transmission settings; and screening of natural local products for insecticidal and repellant properties.
- **Health systems research including social science** - improvement of the home management of malaria based on community knowledge and practices; development and adaptation of products to enhance the case management of malaria at household level; improvement of collaboration between public and private health providers and the exploration of health sector reforms to enhance malaria control strategies.



In the first competition for awards, 64 applications were evaluated and fifteen were awarded. These fifteen which most of those present here are familiar with, cover a range of research priorities identified by the Task force. One important focus is on drug resistance

and there are now five centres that have been supported (see figure above) that will be building capacity to establish data on the profile of drug utilization in patients, the profile of drug resistance in parasites populations, and the molecular profile that can be correlated with drug resistance. It is hoped that with this network led by African scientists and control managers, the future utilization of antimalarial drugs will be more effective, based on local evidence and data.

I would like at this point to thank those who have contributed to the MIM/TDR fund. The initial fund that was used was contributed by the US National Institutes of Health, WHO/TDR, the Government of Norway, the Rockefeller Foundation, the World Bank, the African Regional Office of WHO (AFRO), the French Ministry of Co-operation, the Division for the Control of Tropical Diseases (CTD) at WHO, the Government of Japan and the Roll Back Malaria Project of WHO. In order to move the agenda forward for building capacity in Africa, what is needed now is not only to support funding agencies to continue their input into the MIM programme, but also for African scientists themselves to understand the philosophy underlying the programme, believe in it, promote it and practice it. I hope we will be able to achieve this.
Thank you.

Post-script

Following the MIM Conference the MIM/TDR Task Force convened to consider a second round of applications and to review progress on projects awarded in the first competition. A total of 106 proposals have been reviewed in the two rounds. Twenty projects have been supported, involving 23 African countries, 7 European countries and the USA. Over 100 research groups are involved in total. The provision of training is an important aspect of the MIM awards and 17 PhD and 11 Masters research Training Grants have been approved in connection with the funded projects.

The successful projects supported by the MIM/TDR Task Force on Malaria Research Capability Strengthening in Africa are listed below and full details can be found at:
http://www.who.int/tdr/diseases/malaria/mimprojects.htm.

ADENIYI, J. - College of Medicine, University of Ibadan, Nigeria - Incorporating socio-cultural/economic characteristics of mothers/care-givers in home management of childhood malaria.

AKOGBETO, MC. - Network to study factors conditioning evolution of

pyrethroid resistance in Anopheles gambiae s.l..- Organisation de Coordination de la Cooperation pour la Lutte contre les Grandes Endemies (OCCGE), Cotonou, Benin

AJAIYEOBA, E. - PIMRAT, University of Ibadan, Nigeria - Identification and clinical evaluation of potential antimalarial components from Nigerian phytomedicine compendium.

AKANMORI, B. - Noguchi Institute, Ghana - Immunopathology of severe anaemia in P. falciparum infected children.

DOUMBO, O. - University of Mali - Surveillance and control of drug resistant malaria.

DOSSOU-YOVO, J. - Institute Pierre Richet, Organisation de CoopTration et de Coordination pour la Lutte contre les Grandes EndTmies (OCCGE), Bouake, Ivory Coast - Influence of environment modification for rice cultivation on malaria transmission and morbidity in rural IVC forests.

HASSANALI, A. - R&D partnership in bioprospecting for antimalarial, mosquito repellent & insecticide plants in East Africa. International Centre of Insect Physiology and Ecology (ICIPE), Nairobi, Kenya.

KOKWARO, G. - University of Nairobi, Kenya - Integrated training/research project on clinical pharmacology of key drugs used to treat and manage P. falciparum malaria.

KORAM, K - Noguchi Institute, Ghana - Mapping response of P. falciparum to chloroquine and other antimalarial drugs in Ghana.

LE SUEUR, D. - National Malaria Research Programme, South Africa - Mapping malaria risk in Africa (MARA).

MACHESO, A. - Community Health Services Unit (CHSU), MOH, Malawi - Optimal antimalarial drug policies in Malawi Ministry of Health. Monitoring and limiting evolution of resistance to widely used drugs.

MSHINDA, H. - National Institute of Medical Research, Ifakara, Tanzania - Molecular epidemiology and modelling the spread of antimalarial drug resistance.

NWAGWU, M. - University of Ibadan, Nigeria - Antibodies that inhibit malaria merozoite surface protein-1 processing and erythrocyte invasion.

SANOGO E - Relation between malaria transmission intensity and clinical malaria, immune response and plasmodic index. Centre National de Lutte Contre le Paludisme (CNLP), Ouagadougou, Burkina Faso

NTOUMI, F. - Centre International de Recherches MTdicales (CIRM), Franceville, Gabon - Relation between complexity of infections, disease, transmission and human red blood polymorphism in two African countries.

OKETCH-RABAH H.A. - Research and development of new botanical antimalarial drugs in East Africa. University of Nairobi, Kenya

OLADEPO, O. - Postgraduate Institute for Medical Research and Training (PIMRAT), College of Medicine, University of Ibadan, Nigeria - Intersectoral model for management, control, and policy formulation on drug resistance.

SHARP, B. - National Malaria Research Programme, South Africa - Development and implementation of molecular and biochemistry capability for insecticide resistance monitoring and management in South Africa.

VULULE, J. - Kenya Medical Research Institute (KEMRI), Kenya - Population structure of *A. gambiae* and *A. funestus* in Kenya and West Africa.

Introducing the Global Partnership to Roll Back Malaria

David Nabarro, Roll Back Malaria, World Health Organisation, Geneva, Switzerland

I will start by examining the global malaria burden, using figures and facts that are familiar to many of you. I will present a brief history of the Roll Back Malaria initiative, describe the principles of the Roll Back Malaria Partnership and summarize the outline 10-year plan of action for Rolling Back Malaria. The partners involved in rolling back malaria include national governments, development agencies, research groups, commercial entities and non-governmental organisations. I will predict ways in which they will work together and criteria that can be used to judge the success of the partnership. I shall end by indicating some of the challenges and issues to be addressed if we are to be successful: I hope we will be able to discuss these during the conference break-away sessions.

The global malaria burden

The first MIM meeting in Dakar highlighted the need for more data on epidemiological patterns of disease and intensifying research in this area. Organisations within MIM networks are providing vital information that's important for the future of efforts to Roll Back Malaria: this represents a strong partnership between the research and the control communities.

For example, recent analysis by groups based at KEMRI, with the involvement of the Wellcome Trust team, particularly Dr Bob Snow, have confirmed that we have strong epidemiological basis for the estimate that at least a million people die from malaria each year. 95% of these deaths are in Africa. When deaths due to epidemic malaria are taken into account the total figure will be greater.

We can also be more precise about the other impacts of malarial disease -- particularly its economic impact. Dr Geoff Sachs and his colleagues at Harvard have reminded us that malaria has its greatest impact on the poor people of the world. If we look at countries' GNP per capita and then compare it loosely with the intensity with which they are affected by malaria, we find that intensity is greatest in the poorest countries in the world.

More recent data also suggests that malaria is a major contributor to continuing poverty. This indicates the contribution of malaria to poverty, the economic consequences of the infection, and the contribution of malaria to overload in health sectors.

More of this kind of work is needed. It is critically important that we all have access to more precise data on the epidemiology of malaria and on its impact on economies and societies. The ranges of the estimates that we have for the malaria burden are very great. Unless we can get more precision on the situation, we will find it hard to obtain a realistic understanding of progress with rolling back malaria.

Political support

The Roll Back Malaria initiative recognises that levels of malaria-related mortality and suffering, particularly among the children of Africa, are increasing, and that this undermines development. It builds on the successes of past control efforts, intensifying the response to a level concomitant with the challenge.

The partnership to Roll Back Malaria has profound political support from the Heads of State in the Organization for African Unity who proposed a new initiative on malaria as early as 1994 and declared an intention to reduce the malaria burden for their people in Harare in 1995. This prompted accelerated efforts to control malaria in Africa from 1995 through to the present, led by WHO's Regional Director for Africa, Dr Ebrahim Samba, and his WHO colleagues. They proposed an African Malaria Initiative in 1997.

Recent progress

When Dr Gro Harlem Brundtland was preparing to run for office as Director General at the World Health Organization in late 1997, African leaders convinced her that a greater international effort to tackle malaria was well overdue. She recognised that this would be no easy task, and decided that a novel approach was essential. She announced the Roll Back Malaria Initiative in January 1998 and started preparatory work in February. The initiative was backed both by the World Health Assembly and the G8 heads of State in 1998[2]. A special "Cabinet" project was set up to take forward the WHO contribution to rolling back malaria in July 1998. In October 1998, Dr Brundtland, James Gustaf Speth (then Administrator of UNDP), James Wolfensohn (President of the World Bank) and Carol Bellamy (Executive Director of UNICEF) committed their organizations to rolling back malaria within the next decade. The institutional commitment is absolute, and means that the partnership will support a movement to Roll Back Malaria at community, national, regional and global levels. The global Roll Back Malaria Partnership was consolidated in December 1998. It comprises at least 40 governments of malaria endemic countries, NGOs, development agencies and research groups. WHO's Roll Back Malaria Cabinet Project serves as the secretariat for this partnership.

The present response to malaria is characterised by fragmented efforts among development partners. MIM is one example of a powerful attempt to establish a more focused and synergistic response in the research community. However, the fragmented approach in the malaria control community favours the parasite and the mosquito: it works against the interests of people at risk. Partners want the Roll Back Malaria initiative to put the primary emphasis on people, and not concentrate on the parasite and the mosquito. In proposing principles to the partnership, we in the WHO project are suggesting that if people at risk have the necessary knowledge about malaria and other communicable diseases they are in a better position to make better choices about their health. The choices that they make in practice are also influenced by the way in which they use the knowledge, the supportiveness of their environment, resources at their disposal and services that are on offer. If people are at the centre of Roll Back Malaria, the movement has a chance of maintaining its momentum.

The partners are approaching malaria differently: they see it not just as a tropical disease, not just as an illness, but as a significant cause of world poverty and suffering. This has already been emphasised by speakers in the conference opening ceremony: malaria is a challenge to human development.

Partnership principles

The Roll Back Malaria movement is characterised by other principles too. It is concerned with partnerships, just like MIM – primarily partnerships at the country and community

[2] The G8 includes Canada, France, Germany, Italy, Japan, Russia, United Kingdom and USA

levels, because countries are the place where the majority of control efforts have to be started. It prioritises malaria
appropriately within the health sector development, bridging the gulf which has grown between thoase committed to individual disease control efforts, and those concerned with investing in improved health services. The response to malaria is more clearly defined with an agreed strategy and clear deliverables that should enable those less familiar with malaria to be in a better position to make programme choices. Countries will be enabled to build up their own technical capacities as appropriate and access consistent technical support that is based on the most recent evidence. There is likely to be a strong involvement of the research community and private sector in the Roll Back Malaria effort, both in action at the country level, and in the kind of networks with which you're involved with in MIM. It is hoped that this approach will be a pathfinder for work on other communicable diseases.

Strategy

The Roll Back Malaria strategy has two clear aims: the first to ensure that the existing techniques and interventions to tackle malaria are more effectively used; the second to make sure that new, cost-effective products and interventions are made available. It is based on the Global Malaria Control Strategy, agreed in Amsterdam in 1992. If taken to scale, existing interventions could achieve much better results. In some situations, particularly areas of high *plasmodium falciparum* transmission, significant gains will depend on cost effective new products and tools. A malaria vaccine is needed, and there are promising candidates, though much more research is needed to bring them into use within the next 10 years. New combination drugs, such as artemisinin derivatives, will be essential to reduce mortality and combat drug resistance. More anti-malarial products are needed, at an affordable price, given the capacity of the parasite to resist so many of those which are currently available.

The strategy will be presented in a simplified form: the prototype is in the circular booklet that is being made available to conference delegates for their comments. There are several principles that underlie the strategy: first - Roll Back Malaria is about choosing the appropriate response to local needs. There is no single approach to malaria that is applicable everywhere. Second, that Roll Back Malaria as a global movement that catalyses local initiatives. It is built up on the capacity and ideas that are expressed by communities and countries. It involves local partnerships and local initiatives working towards common goals. It is not a global movement with a global blueprint.

There are six elements to the strategy: six elements to what we all do if we're involved in malaria work. We are now trying to capture these in a short form which will enable a wider understanding of the strategy: I present the first attempt to do this now, as we would like help from the research community to develop it further. The essential elements include **evidence-based decisions, with an emphasis on prompt detection and early treatment, multiple approaches to prevention, effectively coordinated action (within the context of a stronger health sector) and a dynamic global movement.**

Examples of **evidence-based decision making** include

- better surveillance of malaria in populations (using patient and community studies as well as climate-related GIS studies) to detect and respond to areas and populations most at risk;

- monitoring of the malaria parasite's resistance to anti-malarials, so as to establish the most appropriate policies for drug therapy, and
- communities having reliable information about malaria so that they can make choices about how to respond that safeguard their health.

The need for **prompt diagnosis and rapid treatment** is well recognised among malaria professionals. The strategy recognises that

- home is the first hospital – giventhe speed at which malaria kills, it's vital to have the medicines and interventions available within or close to the home, especially for children.
- treatment for severe malaria needs to be to close to where the people live rather than many hours' travel time away. This may mean ensuring that local healers and private practitioners are better able to respond to malaria, and
- effective referral services for the severely ill at local hospitals are essential, if lives are to be saved.

We need to encourage the selection of the best **combination of approaches to prevention** . For example, researchers in this room have shown that in some settings, particularly where transmission is intense, bednets and other materials treated with insecticides can yield incredible results. They can reduce childhood malaria deaths by at least 20%, perhaps even by 25% or 30%. Other methods include the spraying of safe insecticides onto house walls (especially important in situations of epidemic malaria), the location of home, animals sleeping close to the house as decoys, and mosquito coils. Communities that are well planned with good environmental management limit mosquito breeding. Multiple approaches to prevention are key.

The partnership will need to support **strategic research** to develop new treatments, vaccines and insecticides, through imaginative new ventures that encourage greater involvement of industry, and co-ordinated efforts to develop a malaria vaccine.

Action to roll back malaria has to be coordinated . The strategy recognises three components to this action: community action, health sector development, and the involvement of other sectors of government in getting results: sectors concerned with education, industry, agriculture and the environment.

A **dynamic and effective movement** , involving a coalition of stakeholders working in partnership, is the only way to take forward action to roll back malaria. Stakeholders include national governments, commercial entities, foundations and trusts, non-governmental organizations, civil-society associations and media, research and academic institutions, UN organisations, development banks, bilateral development agencies, NGOs and civil society. Action is most effective if they are able to work together in partnership, and national governments should lead these partnerships. The World Health Organization will offer technical support. Such partnerships are likely to emerge in malaria-affected countries over the next several years.

Taking forward action to Roll Back malaria

The objective is to halve the global malaria burden over the next ten years through a mixture of interventions adapted to local needs made available through community level action and supported by more effective health care systems. This will be achieved through

intensified action at community level, supported within countries by the partners working together. They will adopt harmonized strategies and ensure consistent approaches to capacity building and addressing technical issues. Partners will also undertake intensive investment in better control tools.

Inception of country-level action to roll back malaria involves national governments and outside agencies working together to establish partnerships that are collectively committed to RBM action. During the first year partners will reach agreement on ways to work together that respect the comparative advantage of each, and involve working together in a flexible manner towards common goals using agreed strategies and procedures. We expect to see Roll Back Malaria action incorporated into a wide range of health sector and inter-sectoral initiatives. We hope it will be possible to institutionalise the partnership procedures within countries as soon as possible, while adopting flexible approaches to catalysing community-wide movements. We expect to see a range of imaginative and novel approaches taken forward through the efforts to committed advocates who are not normally involved in health action.

Already the World Bank, UNICEF, and bilateral donors are working with a number of governments in Africa to establish partnerships. Key officials within government and development agency offices are teaming up together to help catalyse national RBM movements. During the remainder of 1999, WHO country, regional, headquarters offices will be heavily involved in initiating this action. This will mean working with partners to establish the current situation, agree intentions for RBM at country level, initiate advocacy, and set up systems for monitoring progress. WHO will provide specific support to country partnerships - trying to broker technical and financial assistance, endorsing the technical content of strategies based on the best practice, encouraging partners to stick to their agreements and monitoring progress within the context of wider health sector development.

The Global Partnership will meet regularly (twice yearly at first) to focus on country-level needs and the needs for investing in research and product development. This means a particular focus on what's happening at the country level, and intense efforts to achieve a significant increase in resources. The partnership met for the first time in Geneva during December 1998. Within WHO, we plan a single WHO-wide strategy for rolling back malaria, with partners eventually subscribing to this strategy to ensure harmony and consistency. Roll Back Malaria will support a number of technical support networks based on WHO regional offices, and involving personnel from other development agencies as relevant. One example is the technical support network on insecticide treated materials which will be handled by UNICEF, with strong sponsorship and support from WHO.

Support networks to develop capacity for rolling back malaria

The WHO Roll Back Malaria Project will draw on capacity throughout WHO at all levels: we hope that within a few months, WHO county representatives, regional office personnel, and personnel from headquarter departments offer the same core information and approach to rolling back malaria. We expect the technical support networks to build on existing efforts of the research and consulting communities - the kind of areas that MIM has taken as its priorities. This means technical support for

Increasing the use of insecticide treated materials,

Effective home management of people with possible malaria,
Establishing treatment policies in the face of anti-malarial resistance,
Improving access to quality anti-malaria drugs,
Mapping malaria prevalence and predicting epidemics, and – importantly –
Tackling malaria within the context of complex emergencies.

Investments in intervention research and product development

The Roll Back Malaria project will try to establish an umbrella within which partners feel inspired to increase their strategic investments in better tools for rolling back malaria. This should result in

- Increasing support for priority intervention research within African institutions,
- Greater investment in the work of co-sponsored Tropical Disease Research programme,
- Effective synergy between the Roll Back Malaria initiative and MIM, and
- Political and financial backing for the new Medicines for Malaria Venture.
- Catalysis of other partnerships that involve commercial entities developing and marketing promising new products and making them accessible to those who need them.

We join others in proposing that it is now time for a new initiative to focus and co-ordinate the research effort to develop an effective malaria vaccine.

Criteria for judging the success of the roll back malaria partnership

Several criteria have been developed for judging the success of the Roll Back Malaria Partnership:
To what degree are country partnerships are being developed and owned by national authorities?
To what degree are strategies harmonized? Is technical guidance consistent and useful?
How well is the global partnership working?
Are issues of health sector development being taken into account at community and country level?
Is there additional strategic investment in research and product development?
To what extent are populations as a whole able to access better treatment, better protection?
In the longer term, is there evidence of a decline in malaria-related mortality and morbidity.

Success in rolling back malaria will only be possible if there is the fullest possible interaction and cooperation between the "control" community and researchers, and if researchers continue to ask tough questions about the intentions, technical strategy, programme plans and proposed outcomes for RBM. We will seek to institutionalise dialogue between the two communities during 1999-2000.

Principles that underlie the RBM initiative

Roll Back Malaria is not a project. Nor is it a programme. It is a movement -- a movement supported by a range of partners, and owned by the communities who contribute to the movement. I hope that the research community, and MIM, will become stakeholders in the RBM movement. Although decisions within the RBM global partnership are made by consensus, they are guided by a series of principles. One of these is that country priorities drive Roll Back Malaria. The partners will function independently yet in concert, and they will contribute where they have a comparative advantage or interest. At all stages, action

plans for all involved in rolling back malaria should be clear, science based, prioritized and adapted to local realities. Action to roll back malaria will involve broadening and strengthening the capacity of health sectors to fight all diseases. The ultimate objective is to reduce poverty and promote human development.

Challenges that we face: priorities for 1999

We face several substantial challenges. These include:

- Establishing a consistent world wide approach for rolling back malaria
- Ensuring that national authorities are in the lead
- Encouraging partners to respond to local situations in ways that reflect the local needs,
- Making maximum use of control tools that have been developed and tested at local level.
- Raising substantial additional resources -- $300 million per year extra for malaria related activity in Africa alone
- Ensuring that there is good investment in strategic and operational research – of the kind being encouraged by MIM
- Ensure that the new Medicines for Malaria venture is properly capitalized and can begin discovering and "proving the principle" of potential new antimalarials.

Priorities for the Roll Back Malaria project this year include

- developing the RBM concept,
- undertaking advocacy,
- mobilising resources,
- building the global partnership, and
- activating country level action.

Consensus building and inception

A series of consensus building and inception meetings, led by the WHO regional offices, is planned during the next three months. Intense efforts will be initiated

- to promote consistent support for capacity development and technical guidance
- to get more support into research and development and
- to monitor progress.

Over the next few days, I hope that colleagues here will join the effort to establish consensus around the Roll Back Malaria initiative. Do we agree that the goal is feasible, and the approach is valid? Can the approach be put into practice using current institutional arrangements? If not, what must be changed? How can we best build on ongoing activities, take account of research and other findings, and contribute to development of effective health sectors? How can we make sure that up to date information is available on what is happening? How to offer flexible technical support in a responsive manner, and procedures for mobilising resources? How to ensure that WHO itself is able to respond to the challenge?

Conclusion

We face a unique challenge. We have an extraordinary, once in a life-time, opportunity. There is a huge political momentum now to try once again to make a real difference to the malaria burden faced by the people of our world. After several months of analysis, synthesis and dialogue, I conclude that we can succeed. We **will** succeed if we focus relentlessly on the needs of millions of people, and dozens of countries, whose

development is undermined by malaria. That focus will inspire us to establish consensus, and then to work in synergy and true partnership. It may not be an easy task, but the prize is really worth fighting for. Let's get rolling.

At the start of his presentation, Dr Nabarro indicated that by March 1999, at least fifteen African Heads of State together with six governments in South East Asia were committed to the success of the global partnership to Roll Back Malaria. He then introduced a number of participants at the meeting who represented organisations involved in the partnership. They included Dr Welele Shasha, representing Dr Samba, WHO's Regional Director for the African Region; Dr Yao Kassankogno who leads the Malaria team in the WHO Africa Regional Office, and Dr Doyin Oluwale representing the Integrated Management of Childhood Illness team in the WHO Africa Region; Dr Ok Pannenborg, who represented the World Bank and Dr Kopano Mukelabai who represented UNICEF; Dr Dennis Carroll representing the United States Agency for International Development, Dr Guiseppe Masala and Dr Giancarlo Maiori, representing the Government of Italy; Caroline Sargeant, representing the UK Government; Dr Eva Maria Christophel from the University of Munich, who works on malaria with the German Government's international development assistance programme; and Dr Mary Galinski who represents the International Malaria Foundation. He paid tribute to Tore Godal, of WHO, who nurtured the Roll Back Malaria partnership to where it is at this time, and was the first manager of the WHO Roll Back Malaria project. He indicated that professional colleagues working within WHO, national governments and other partner organisations undertook much of the work being described.

BREAKOUT SESSIONS: MALARIA CONTROL AND ROLL BACK MALARIA

Programme

1. Malaria Control and RBM

Chair: Professor Marcel Tanner

Rapporteurs: Dr. Melville George, Dr. Halima Mwenesi

1. Putting Roll Back Malaria into Practice: An introduction - David Nabarro
2. Advocacy and Global partnership to Roll Back Malaria - Kopano Mukelabai
3. Overview of the Country needs assessment within RBM-AIM - Hans Remme
4. World Bank/WHO/UNICEF country needs assessment - J. McLaughlin
5. Health Sector development within the context of RBM-AIM - James Banda

2. Malaria Control and RBM

Chair: Dr Yao Kassankogno

Rapporteurs: Dr. James Banda, Dr Christian Lengeler

1. Funding mechanisms - John P. Clark and David Nabarro
2. Implementation of RBM-AIM - Raphael Gbary.
3. Capacity Building in Africa Region for Malaria control - Oladapo Walker.
4. Operational research within control programmes - Robert Guiguemdé

3. Malaria Control and RBM

Chair: Dr. Guy Barnish

Rapporteurs: Dr. Penny Phillips-Howard, Professor Oladapo Walker

1. Resource Networks within the context of RBM-AIM - Fred Binka
2. Indicators, monitoring and evaluation - Edwin Afari
3. Case control approaches to mortality impact - Jo Schellenberg
4. Measuring behavioural change during interventions - Margaret Gyapong

ANTI MALARIAL DRUGS

Plenary Presentations

Impact of drug resistance on morbidity and mortality.
Jean-Francois Trape

Factors leading to the development of antimalarial drug resistance.
Nicholas J White

Antimalarial drug policies and resistance : current issues.
Sylvia Meek

Country priorities and plans for chemotherapy for malaria control in Africa.
Oladapo Walker

Collaborations to address the challenge of antimalarial drug resistance.
Peter Bloland

Breakout Sessions

Programme

1. Meeting Challenges with Antimalarial Drugs in Africa.

2. African Scientists and Institutions in Developing Drugs for Malaria.

3. Joint Session: Management of Severe Malaria and Antimalarial Drugs

Summary Report

PLENARY PRESENTATIONS

Impact of Drug Resistance on Morbidity & Mortality in Malaria Infections in Africa

Jean-François Trape, Laboratoire de Paludologie, Institut de Recherche pour le Développement (IRD, formerly ORSTOM), France.

Introduction

Chloroquine-resistant strains of *P. falciparum* were first observed during 1978 in East Africa. Between 1978 and 1988, resistant parasites have been reported in all countries of tropical Africa. In each newly affected country, chloroquine resistance has progressed in three different ways: (1) it has spread in a growing number of locations and regions in the country; (2) the prevalence of resistant strains in each area has increased; (3) the degree of resistance has intensified, with a relative reduction in RI type responses in favour of RII and RIII type responses. Despite high levels of resistance, chloroquine remains in 1999 the first line treatment for malaria attacks in most African countries. A number of studies have reported that patients infected with resistant strains improved clinically within a few days when receiving chloroquine, and this has lead to the assumption that chloroquine retains sufficient efficacy to justify its use even though a high proportion of children remain parasitemic after treatment. In this paper, we review hospital and community-based studies conducted in Africa over the past fifteen years. There is now clear evidence that chloroquine resistance has had a dramatic impact on morbidity and mortality in malaria infections in Africa.

Hospital-based studies

The first evidence of increasing malaria morbidity and mortality temporally related to the emergence of chloroquine resistance came from National health statistics of hospital admissions and deaths in Malawi. During the period 1978-1983, the incidence of admissions for malaria among children under 5 years of age more than doubled, with the case fatality rate remaining relatively constant and averaging 5% (Khoromana *et al.*, 1986). Case reports of chloroquine prophylaxis failure in nonimmune visitors to Malawi had substantiated local emergence of resistant *P. falciparum* during this period (Overbosch *et al.*, 1984; Fogh *et al.*, 1984), and studies among Malawian children conducted in 1984 at six surveillance sites indicated that on average 57% of children were parasitemic on Day 7 after standard malaria therapy with chloroquine (Khoromana *et al.*, 1986).

A second evidence came from a study by Greenberg *et al.* (1989) in Zaire. This study was conducted at Mama Yemo Hospital, which was the largest medical centre in Kinshasa and served as a referral centre for patients with severe malaria who have not responded to antimalarial therapy either at home or at one of the many clinics in the city. From 1982 to 1986, the total number of paediatric admissions and deaths remained relatively constant, but the proportional malaria admission rate increased significantly from 29.5% in 1983, 41.7% in 1984 and 45.6% in 1985 to 56.4% in 1986, and the proportionnal malaria mortality rate, from 4.8% in 1982, 7.0% in 1983, 7.9% in 1984 and 8.9% in 1985 to 15.3% in 1986. During this period, there were no significant changes in diagnostic capabilities or in medical personnel at the hospital that could account for the results. However, chloroquine-resistant *P. falciparum* malaria emerged in Kinshasa during the 5-year study interval. In 1982, no case of *in vivo* or *in vitro* chloroquine-resistant malaria was detected in Kinshasa (Nguyen-Dinh *et al.*, 1985). The first evidence of *in vivo* chloroquine resistance in the city was observed in 1984 (Ngimbi *et al.*, 1985), and by 1985 a total of 56% of *P. falciparum* infections in Kinshasa children were not cured by a standard regimen of 25 mg/kg chloroquine (Paluku *et al.*, 1988). By 1986, a total of 82% of *P. falciparum* parasites isolated from children at Mama Yemo Hospital exhibited *in vitro* resistance to the drug (Nguyen-Dinh *et al.*, 1987).

Chloroquine resistance emerged in Congo in 1985 (Carme *et al.* 1990). In December 1985, 39% of Brazzaville children were not cured by 25 mg/kg chloroquine. Trends in the incidence of malaria admissions and cerebral malaria deaths in the four hospitals of Brazzaville during the period 1983-1989 were studied by Carme *et al.* (1992a). From 1983 to 1986, malaria

admissions increased from 22% to 54% of total paediatric admissions and stabilized the following years. Cerebral malaria deaths more than doubled during the period 1986-1989 compared to the period 1983-1985.

During the period 1986-1988, an upsurge of malaria-related convulsions was observed in the paediatric emergency room of Calabar Hospital, Nigeria, and the number of cerebral malaria cases more than doubled (Asindi *et al.*, 1993). The increase in the incidence of cerebral malaria corresponded to the emergence of chloroquine resistance in this area of Nigeria. A high proportion of children (81%) who were hospitalized in 1988 for malaria-related convulsions did not respond to chloroquine.

After the emergence of chloroquine resistance, a study in a district hospital in Kenya indicated that among children hospitalized for malaria, the risk of dying was associated with the antimalarial treatment received. Children who received treatment with a regimen that would clear parasitaemia (either sulfadoxine-pyrimethamine, quinine, or a five days of sulfamethoxazole-trimethoprim) had a 11% case fatality rate within 8-weeks of hospitalization compared with a 33% case-fatality-rate among children who received chloroquine (Zucker *et al.*, 1996). Because of the striking effect of treatment on survival from malaria, sulfadoxine-pyrimethamine was provided as first line therapy of children admitted to that hospital with malaria beginning in February 1992. The case-fatality rates decreased from 9.9% in 1991 to 5.1%, 3.6%, and 3.3% in 1992, 1993, and 1994, respectively (Zucker *et al*, unpublished).

In absence of malaria treatment, anaemia is a frequent complication of *P. falciparum* attacks in young children. In the past, severe malarial anaemia was the leading cause of malaria deaths in areas of central Africa with limited access to antimalarial drugs (Kivits, 1951), but its incidence decreased considerably when chloroquine became widely used (Trape *et al.*, 1987 and unpublished). Since the 1980's, numerous studies have reported a high incidence of severe malarial anaemia among hospitalized children, and most of these studies were conducted in areas with high levels of chloroquine resistance. In Banjul, The Gambia, a prospective study of 9584 consecutive paediatric admissions to the Royal Victoria Hospital was conducted over 3 years, from 1988 to 1990, when chloroquine resistance was emerging. During the study, there was a 27% annual increase in severe anaemia owing to malaria (Brewster & Greenwood, 1993). In Western Kenya, severe anaemia has become a major cause of malaria death in young children after the emergence of chloroquine resistance, and the risk of dying from severe malarial anaemia was significantly higher for children treated with chloroquine than for children receiving other antimalarials (Zucker *et al.*, 1996).

Population studies

In Senegal, long-term demographic surveillance programmes were initiated in three rural areas of the country between 1963 and 1984. Since 1984, a continuous study of the causes of death has been added to the registration of demographic events and specific data on malaria have been collected in each area (Sokhna *et al.*, 1997; Trape *et al.*, 1998). These programmes were conducted in Mlomp (rain forest, 11 villages, 7,287 inhabitants in 1995), Niakhar (Sahel, 30 villages, 28,246 inhabitants in 1995), and Bandafassi (Sudan savanna, 38 villages, 8,612 inhabitants in 1995). All deaths which occurred among the three study populations were investigated using the verbal autopsy technique and available data from medical source. Levels of chloroquine-resistance were determined by *in vivo* tests and over twelve years, from 1984 to 1995, malaria specific mortality was studied prospectively. The first therapeutic failures with chloroquine were observed in 1990 in Mlomp, in 1992 in Niakhar, and in 1993 in Bandafassi. The following years, standardised surveys documented the intensification of chloroquine resistance. High levels of chloroquine resistance appeared rapidly in Mlomp (RII/RIII: 36% in 1991, 30% in 1992, 41% in 1994, 46% in 1995). Chloroquine resistance progressed less rapidly in Niakhar (RII/RIII: 10% in 1993, 15% in 1994, 17% in 1995, 29% in 1996) and in Bandafassi (RII: 6% in 1994, 16% in 1995). The emergence of chloroquine resistance has been associated with a dramatic increase in malaria mortality in each of the studied populations (Trape *et al.*, 1998). In Mlomp, where malaria was hypoendemic and child mortality was low as a result of the widespread use of chloroquine for prophylaxis and treatment and important health programs, malaria became mesoendemic and the incidence of malaria deaths in

children under ten has risen 5.5 fold. The increase in malaria mortality was particularly dramatic among children under five, with 0.5, 3.4 and 5.5 deaths per thousand children per year for the periods 1985-1989, 1990-1992 and 1993-1995, respectively. In Bandafassi, a holoendemic area where access to health care was limited, mortality attributable to malaria in children under five has risen 2.5 fold, from 4.2 to 11.4 per thousand per year for the periods 1984-1992 and 1993-1995, respectively. In Niakhar, a mesoendemic area, where malaria transmission was the lowest of the three study areas, mortality attributable to malaria in children under ten has doubled, from 4.0 to 8.2 per thousand per year for the periods 1984-1991 and 1992-1995, respectively.

Except in Senegal, studies of malaria mortality at the community level in Africa either have been short term or were initiated after the emergence of chloroquine resistance. In a site in a rural area of coastal Tanzania where mortality rates and causes of death were investigated during the years 1984-1985 and 1992-1994, overall child mortality remained unchanged between the two surveys despite the introduction of a sucessful immunization programme and a village health system. The proportion of deaths attributed to malaria was 2-fold higher during the most recent study (Mtango & Neuvians, 1986; Premji *et al.*, 1997).

Indirect malaria mortality and impact on diseases other than malaria

In most areas of tropical Africa, chloroquine chemoprophylaxis is now poorly effective for preventing *P. falciparum* infections during pregnancy. Malaria in the pregnant women increases the risk of low birth weight which represents the greatest single risk factor for neonatal and early infant mortality (Jelliffe, 1968; McGregor *et al.*, 1983; Brabin, 1991; McCormick, 1985). This suggest that chloroquine resistance may also have resulted in higher levels of infant mortality through decreased efficacy of chemoprophylaxis recommanded to pregnant women (Steketee *et al.*, 1996).

It has been a general observation from malaria control programmes through DDT spraying, impregnated bednets and chemoprophylaxis that effective malaria control may prevent more deaths than the number of deaths previously attributed to malaria in the same population (Najera & Hempel, 1996). One reason is the contribution of the health services, created or improved for malaria control, to the management of other health problems as well as to the general health information and education of the population. However, another probable factor is that malaria affects the capacity of the organism to resist concomitant diseases. It has been shown that drug resistance is an important factor in producing anaemia or preventing optimal haematologic recovery in children receiving non-effective malaria treatment (Bloland *et al.*, 1993; Slutsker *et al.*, 1994). It is likely that the case-fatality of certain diseases increases in the presence of malaria-associated anaemia which is related to the intensity and duration of parasitaemia (Greenwood, 1987; Bradley-Moore *et al.*, 1985)

Blood transfusions are widely used in referral hospitals to treat severe anaemia, and this is likely to constitute a cause of HIV contamination of young chidren. The association between malaria, blood transfusions, and HIV seropositivity was investigated in Kinshasa by Greenberg *et al.* (1988). Malaria was the most frequent indication for blood transfusions in both hospitalized and emergency ward pediatric patients. The emergence of chloroquine resistance was associated to a 2-fold increase of the number of blood transfusions, and a strong positive association between transfusions and HIV seropositivity was detected. Compared with children who received no transfusion, children who received one transfusion were 2.8 times as likely to be HIV seropositive, those who received two transfusions were 7.9 times as likely to be HIV seropositive, and those who received three transfusions were 21.9 times as likely to be HIV seropositive.

For most African countries, there are no national data on causes of death. However, information on the levels and trends of overall child mortality are often available at the national level from surveys and censuses. In the case of Senegal, the risk that a new born child die before the age of 5 declined to 287, 236, 191 and 131 per thousand during the periods 1971-1975, 1976-1980, 1981-1986, and 1988-1992, respectively (Pison *et al.*, 1995). By contrast, the most recent survey indicated that child mortality was 139 per thousand during

the period from March 1992 to March 1997. This change in the national trend was concomitant with the generalization of chloroquine resistance in the whole country, and the increase in malaria mortality observed among three rural study populations, an indication that the recent stop in the decrease of child mortality in Senegal could be related to chloroquine resistant malaria (Trape *et al.*, 1998). In The Gambia, data from population censuses and various other sources showed rapid secular improvements in mortality among those younger than 5 years from the late 1960s to the late 1980s; however, as in Senegal, overall mortality stabilized or even increased in the early 1990s when chloroquine resistance emerged (Hill *et al.*, 1998). Demographic and health surveys in Ivory Cost and Central African Republic indicate similar trends.

Discussion

There is now strong evidence that the emergence and spread of chloroquine resistance has had dramatic public health impact in Africa. Malaria specific mortality has probably doubled or more in most parts of tropical Africa, and it is likely that increased malaria-related anaemia has had significant effects on mortality from other diseases and contributed to HIV dissemination among children. Such dramatic impact was considered as certain by most experts in the 1970's and early 1980's, i.e. before the emergence and spread of chloroquine resistance, and was rapidly confirmed by a hospital-based study in Kinshasa (Greenberg *et al.*, 1989). However, by contrast, many subsequent studies in Africa concluded there was no urgent need to change national policies for the treatment of malaria from chloroquine to alternative drugs.

We believe that two main factors have long masked the real impact of chloroquine resistance. First, only limited data from prospective mortality studies were available. Althought several dozens of community studies of malaria mortality have been conducted in Africa (see review in Snow & Marsh, 1995, and Snow *et al.*, 1999), most of them have been short term and only those conducted in Senegal have collected data in the same community before, during and after the emergence of chloroquine resistance. The number of hospital-based studies which documented the impact of chloroquine resistance was also limited. Second, by contrast, a number of *in vivo* studies of chloroquine efficacy were carried out. With the progression of chloroquine resistance, these studies indicated that an increasing number of patients treated with chloroquine did not clear their parasitaemia, but also that severe complications were rarely seen. Since most patients improved clinically within a few days even in case of parasitological failure, this has lead to the assumption that chloroquine retains sufficient efficacy to justify its use even though a majority of patients remain parasitaemic (Brandling-Bennett *et al.*, 1988; Bloland *et al.*, 1993).

To explain this paradox, it is necessary to consider the potential lethality of each malaria attack occuring among patients living in highly malaria endemic areas. The daily surveillance of cohorts of children in Congo and Senegal has shown that most individuals suffer several dozens of malaria attacks during childhood (Trape *et al.*, 1987; Trape & Rogier, 1996). Over one year, a cohort of 1,000 children aged 0-5 years present about 2,000 to 4,000 malaria attacks according to the entomological inoculation rate. Even when malaria mortality is high, e.g. ten per thousand children per year (as observed in populations with poor access to antimalarials or high levels of chloroquine resistance), this implies that the potential lethality rate of each malaria attack remains very low, since the 990 surviving children totalize from 1,980 to 3,960 malaria attacks during this given year. In the case of the Mlomp study in Senegal, analysis of demographic, epidemiological and clinical data suggested that only one malaria attack in five hundred was lethal in children under five years old after the emergence of chloroquine resistance despite an eleven-fold increase in malaria mortality in this age-group due to chloroquine resistance. The low lethality of malaria attacks under conditions of high endemicity explains why severe complications occur rarely during *in vivo* tests, even when they are conducted among young children and using poorly effective drugs. Furthermore, for evident ethical reasons, most *in vivo* studies of chloroquine efficacy in Africa were carried out under close surveillance among either asymptomatic subjects, or patients belonging to age-groups not exposed to high malaria mortality, or selected children with mild or very mild malaria symptoms.

Since the early 1950's, chloroquine has saved the life of dozens of millions of Africans. There is now strong evidence that the spread of chloroquine resistance has a dramatic public health impact, with many children dying each year because of the use of chloroquine for malaria treatment. There is an urgent need to change treatment policies in Africa.

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[1]Preventing Antimalarial Drug Resistance

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Introduction

The estimated annual mortality from malaria ranges between 0.5 and 2.5 million deaths. The burden of this enormous death toll, and its concomitant morbidity, is borne by the world's poorest countries. It has been said that 90% of the deaths from malaria in the world occur in Africa. Malaria morbidity and mortality in the tropical world have been held in check by the widespread availability of cheap and effective antimalarial drugs. We are now losing these valuable drugs to resistance, and this may represent the single most important threat to the health of people in tropical countries. Chloroquine has been the mainstay of antimalarial drug treatment for the past forty years, but resistance is now widespread throughout the continent of Africa and elsewhere. Few tropical countries are unaffected. Pyrimethamine-sulphadoxine (PSD) is usually the next choice after chloroquine. Both these antimalarials cost less than 20 cents per adult treatment course, but the drugs required to treat multi-drug resistant falciparum malaria (quinine, mefloquine, halofantrine) are over ten times more expensive and these cannot be afforded by most tropical countries - especially those in Africa. Resistance to PSD is increasing, particularly in East Africa. As treatments lose their effectiveness, morbidity and mortality from malaria will rise further. Can this be prevented? Can we really "roll back malaria"?

The rationale for combining drugs with independent modes of action to prevent the emergence of resistance was developed first in anti-tuberculous chemotherapy. The same principle has since been adopted in cancer chemotherapy and, more recently, in the treatment of AIDS and early HIV infection. Now it would not be considered ethical to treat tuberculosis or AIDS with a single drug. The same should apply to the treatment of malaria. This reflects the opinions of many leading researchers in the field of malaria chemotherapy. The principle is simple. Resistance arises from chromosomal mutations in the malaria parasite. The chance that a mutant will emerge that is simultaneously resistant to two different antimalarial drugs is the product of the per parasite mutation rates for the individual drugs, multiplied by the number of parasite[1]s in an infection that are exposed to the drugs. For example if 1 in 10^9 parasites are resistant to drug A and 1 in 10^{13} are resistant to drug B, and the genetic mutations which confer resistance are unlinked, then only 1 in 10^{22} will be resistant simultaneously to both A and B. Most patients ill with malaria have between 10^8 and 10^{12} parasites at presentation, and a biomass of $>10^{13}$ parasites in a single person is physically impossible. In this example therefore, the majority of patients will have at least one parasite resistant to drug A, between 0.1 and 1% will have a parasite resistant to drug B, but a parasite resistant simultaneously to the two drugs would only occur approximately once every 10^{12} treatments (i.e. less than once a century). Thus compared with sequential use of single drugs (current policy), combinations will considerably retard the development of resistance.

Artemisinin and its derivatives (artesunate, artemether, dihydroartemisinin) are the most potent and rapidly acting of all the antimalarial drugs. They reduce the number of infecting malaria parasites by approximately 10,000-fold per asexual (two day) life cycle compared to 100 to 1,000-fold for other antimalarials. Artemisinin and its derivatives are remarkably well tolerated and, so far, no significant resistance has been reported either in clinical isolates or in laboratory experiments. Combinations of artemisinin, or one of its derivatives, with mefloquine or lumefantrine (benflumetol) have proved highly effective even against multi-drug resistant *Plasmodium falciparum* . Combinations achieve cure rates even higher than long courses of artemisinin derivatives used alone. On the North-Western border of Thailand, where the most drug resistant *P falciparum* in the world are found, the systematic use of

[1] This presentation draws heavily on the opinions of several leading authorities, presented in the recently published: White NJ, Nosten F, Looareesuwan S, Watkins WM, Marsh K, Snow RW, Kokwaro G, Ouma J, Hien TT, Molyneux ME, Taylor T, Newbold CI, Ruebush II TK, Danis M, Greenwood BM, Anderson RM, Olliaro P. Averting a malaria disaster. *Lancet* 1999; 353:1965-7.

combination chemotherapy has halted the progression of mefloquine resistance. This has been attributed to two factors. First, combinations ensure high cure rates because three day's treatment with an artemisinin derivative eliminates most of the infection, and the relatively small residuum of parasites remaining is exposed to maximum concentrations of the more slowly eliminated mefloquine. This residuum (a maximum of 10^5 parasites or 0.000001% of the asexual parasites present initially) is all [2]that is exposed to mefloquine alone. Thus because of this rapid reduction in the parasite population within each patient, the selective pressure for the emergence of mutants with reduced mefloquine sensitivity is lessened considerably. Any mefloquine resistant mutants arising in the initial infection would be expected to be eliminated by the artesunate. Second, the artemisinin derivatives reduce gametocyte carriage by approximately 90%. Recrudescent (i.e. resistant) infections are associated with increased gametocyte carriage rates which provides a powerful selection pressure to the spread of resistance. In Thailand, an infection which recrudesces after mefloquine treatment is four times more likely to have patent gametocytaemia than a successfully treated infection. This transmission advantage is prevented by the combination with an artemisinin derivative. These benefits are particularly important in areas of low or unstable transmission where morbidity and mortality are high, and most malaria is treated (as opposed to asymptomatic and therefore not treated). In this epidemiological context the antimalarial drugs are under intense selective pressure and resistance has, in the past, often developed rapidly. In high transmission areas, where infections occur frequently, and are usually asymptomatic in older children and adults, the rapidly eliminated artemisinin derivative will not be able to protect its more slowly eliminated partner during the elimination "tail" of declining blood concentrations. Infections newly acquired during this "tail" will therefore be under selection pressure. But provided the patients with these infections are treated with the combination if they become symptomatic, and provided the combination partner retains some efficacy against any selected mutants, they will usually be cured, and the resistant parasites will not be transmitted. If the infection does not recrudesce to symptomatic levels of parasitaemia, then it is much less likely to develop patent gametocytaemia - and it will not, therefore, be transmitted. The reduction in the risk of selecting resistance in the primary symptomatic infection is not affected by the prevailing level of malaria transmission. Thus we believe that combinations should slow the evolution of drug resistance in all malarious areas. There are additional, and potentially important, benefits to artemisinin combinations. The rapid therapeutic response ensures that patients are able to return to school or work earlier and, even in the unlikely event of complete resistance to the combination drug (in this case mefloquine), a therapeutic response will still occur, i.e. there will not be a high-grade or dangerous failure to respond to treatment.

Our current practice is to deploy antimalarial drugs individually in sequence. When one fails, another is introduced. Unfortunately there are few antimalarials and the evolution of resistance in *Plasmodium falciparum* appears to be faster than the development of new drugs. There are compelling reasons to believe that resistance to the available antimalarial drugs would be slowed or prevented by the addition of artemisinin or one of its derivatives, as has been the case with mefloquine. Combining an artemisinin derivative with chloroquine and PSD in areas where partial sensitivity to these compounds is still retained should extend their useful life.

Several concerns with this approach are now discussed

Will resistance to the artemisinins be encouraged?

If the artemisinin derivatives are so effective in the management of severe malaria then maybe they should be withheld from use in uncomplicated malaria in those areas "where they are not needed", in order to protect them from the development of resistance. However, combination chemotherapy **does** protect the artemisinin derivatives from the development of resistance. If the drugs are always deployed in combination with another, unrelated,

antimalarial then, provided they are at least partially susceptible to the second drug, parasites are never exposed to the antimalarial activity of the artemisinin derivative alone. Furthermore, given the reassuring lack of resistance to date, and the rapid elimination of these drugs such that sub-inhibitory (i.e.selective) blood or plasma concentrations occur for only hours. Parasites either see maximum concentrations -or none at all! It is reasonable to conclude that resistance to this group of drugs will develop relatively slowly . Furthermore artemisinin derivatives are already now widely available in many tropical countries, and their use is usually regulated poorly. This is already providing selective pressure to the emergence of resistance. If these drugs were deployed only in combination with other antimalarials, then artemisinin resistance would develop much more slowly. This mutual protection will result in a considerably longer useful life span for both components in combination antimalarial chemotherapy than if the two components were deployed in sequence. Resistance could be delayed by decades.

Will the cost be prohibitive?

Cost is usually the major factor determining the deployment and use of antimalarial drugs. Many recent cost estimates for the artemisinins have been inflated. Combinations with artemisinin derivatives would, in general, be expected to double the individual patient treatment cost. But increased short term costs should result in overall savings over the longer term. If combination treatment results in a 3 - 5 year extension in the useful lifespan of chloroquine, amodiaquine or PSD (as it has done for mefloquine on the western border of Thailand), then the overall cost would be less than that of deploying the next, more expensive, alternatives (mefloquine, quinine). Many believe resistance would be delayed by much longer if the policy were implemented immediately. As chloroquine and PSD are already failing in many areas, combination treatment would be expected to improve cure rates with a reduction in the morbidity (and thus costs) associated with treatment failure. In areas of low transmission use of the artemisinin derivatives may have the added benefit of reducing the incidence of malaria. In areas of Vietnam and Thailand where these drugs have been deployed there has been a marked reduction in the incidence of falciparum malaria saving both lives and money.

What about toxicity?

In experimental animals intramuscular injections of the oil-based compounds arteether and artemether have induced an unusual and selective pattern of damage to certain brain stem nuclei [12]. This appears to arise from sustained exposure of the central nervous system as a consequence of the very slow absorption of these drugs from the intramuscular site. In contrast, in these experimental animals, the therapeutic ratio is considerably larger after oral administration of these drugs, and, for the water soluble drugs, by any route of administration. This appears to be related to the rapid absorption and elimination after oral administration. There has been no evidence of any adverse neurological effects in a clinical experience extending to several million patients, detailed prospective studies in over 10,000 patients, and neurophysiological evaluations in over 300 subjects who have received multiple treatment courses.

The artemisinin derivatives are remarkably well tolerated antimalarials but combining drugs may lead to unexpected adverse effects. There is no evidence for untoward adverse effects resulting from combinations of artemisinin derivatives with mefloquine, lumefantrine, and in a small study with atovaquone-proguanil. However studies of pharmacokinetics and tolerability are needed on combinations with other available antimalarials (particularly chloroquine, PSD and amodiaquine) and these are now being undertaken. Studies are also needed on the safety of combinations in pregnancy.

What are the Regulatory requirements?

To ensure compliance with drug combinations, the individual components should ideally be formulated together in a single tablet or liquid preparation, but this will necessitate expensive pharmacokinetic, pharmaceutic and toxicological studies required for regulatory approval - and who will pay for these? A less satisfactory but simpler alternative would be to combine

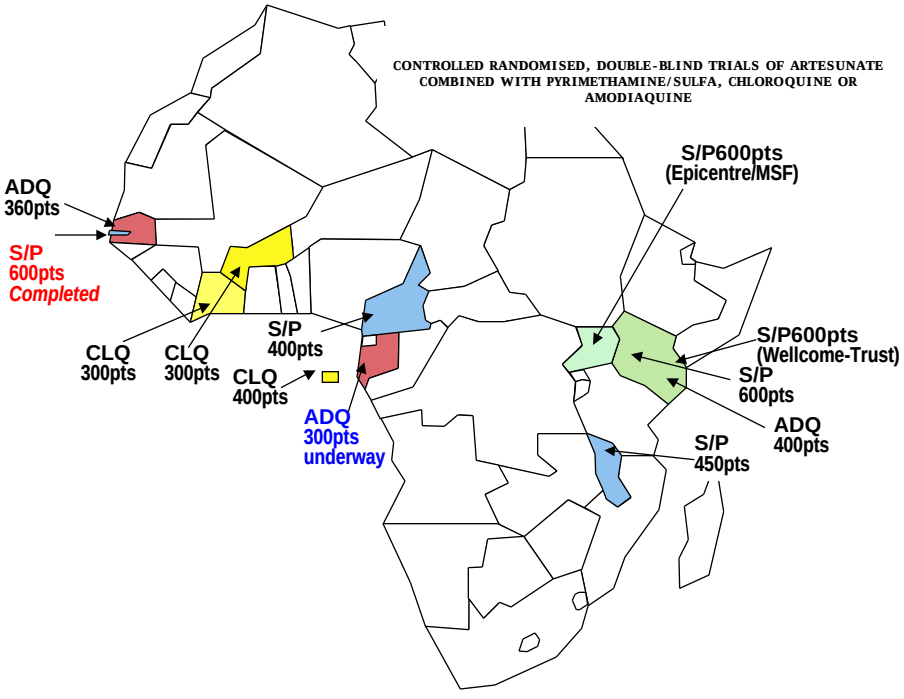
separate components in blister packs as in the multiple drug treatment of tuberculosis and leprosy. The successes of directly observed therapy (DOTS) in these infections may be relevant to antimalarial treatment. The use of combinations should be accompanied by new initiatives to facilitate compliance and to encourage dispensers and shopkeepers to educate their patients on the need to complete a full course of treatment. Wherever possible treatments
hould be observed. More effective surveillance should also be encouraged in tropical countries, both to monitor efficacy and also to document adverse reactions.

What is to be done?

Normally the answer is "more research", and indeed some more research is required as outlined below but, critical decisions often need to be taken with incomplete knowledge. Time is running out in Africa; four countries (Malawi, Kenya Botswana and South Africa) have already been forced to deploy PSD as their first line antimalarial. When this happened in South East Asia high level resistance developed within a few years and mefloquine had to be substituted. For the vast majority of people on the African continent who cannot afford a dollar or more for antimalarial treatment, widespread resistance to PSD or its analogues will be a disaster. Time is running out. In East Africa parasites with up to three mutations in the DHFR gene, conferring antifolate resistance, are already prevalent in some areas. Aquisition of the 164 DHFR mutation, found in SouthEast Asia, would render PSD ineffective. The development of artemisinin resistance would also be a health care catastrophe. Both these disasters could well be averted if the approach outlined in this presentation were to be adopted widely. Buying another five or ten years extra-life for the available affordable antimalarial drugs will allow time for new drugs to be developed and other interventions to be deployed. There are formidable logistic and political barriers to rapid action on the scale required, but many believe that this is now the single most important issue for malaria in Africa.

What is being done?

The Wellcome Trust and the World Health Organisation are funding a series of studies to determine the safety and efficacy of artemisinin derivative containing antimalarial combinations. In Southeast Asia the Wellcome Trust has supported large and detailed studies which have confirmed the safety and efficacy of artesunate (3 days) plus mefloquine combinations and the new fixed dose artemether-lumefantrine combination in the treatment of multidrug resistant falciparum malaria. Studies are underway evaluating artesunate-atovaquone-proguanil. In Africa Wellcome Trust supported studies of artesunate-SP combinations are about to start in Kenya, and it is hoped that studies of chlorproguanil-dapsone-artemisinin derivative combinations will be evaluated soon. The newly formed WHO TDR Task Force on Drug Resistance and Policies is organising large studies across the continent evaluating artesunate/chloroquine, artesunate/amodiaquine, and artesunate/SP combinations in a variety of different drug resistance and transmission intensity settings. This large programme is supported by USAID. It is hoped that by mid 2000 the results of these studies will be available and policy decisions can then be made. Research aimed at optimising the clinical and laboratory assessment of resistance, and also how the research findings can be translated into policy is also underway. Following these studies large evaluations of the impact of combinations on resistance will be conducted as the policy is, hopefully, implemented.



Location of African combination study sites as of March 1999.
CLQ= chloroquine versus artesunate-chloroquine, S/P = sulphadoxine/pyrimethamine vs one day artesunate + S/P vs three days artesunate + S/P, ADQ = amodiaquine versus artesunate-amodiaquine. Several studies are jointly supported.

Antimalarial Drug Policies and Resistance : Current Issues

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Introduction

The purpose of this presentation is to highlight some of the key operational issues related to treatment policy and drug resistance. I subtitled this presentation "A story of ifs and buts" and I think anyone who has been involved in developing treatment policy will understand that sub-title.

A major problem that we are currently facing is that rapidly spreading drug resistance is causing a huge additional burden of disease. Many people in Africa are receiving inadequate treatment for malaria, despite the fact that several very effective drugs exist. So the challenge is how can we ensure that malaria patients receive the most effective treatment that is available and affordable?

Drug Policy Framework

In formulating treatment policies, the first dilemma that we face is that there is more than one goal, and these goals conflict to some extent. The primary goal obviously is to treat the patient effectively, at the very least to remove signs and symptoms, but ideally to clear all the parasites. However, there are important secondary goals, including avoiding the development of drug resistance, and if possible reducing transmission in some areas.

Looking at the context for developing a drug policy, it is dominated in many ways by the issue of access. Obviously the choice of the best drug is critically important, but this is only one element of providing treatment. In most developing countries, 50-90% of households buy drugs in the private market, and there is an interesting example from Tanzania showing that 86% of deaths occurred at home and 46% of deaths occurred without any previous access to health facilities. In the private sector there are major problems with under-dosing, irrational treatment and choice of drugs, poor drug quality and incorrect use of drugs. These are all very common and this limits significantly any policy that only addresses the public sector.

The behaviour of the patient or the carer is another important issue. A mother has to make numerous decisions when her child gets sick with malaria, and understanding this process better is essential for developing a policy that is actually implementable. She must recognise the illness, decide what action to take, how much to spend and then if that first line does not work, go through the whole process again, maybe several times, and possibly each time with the child getting sicker and therefore more costly to treat. A related issue that strongly influences policy implementation is the behaviour of the health care providers,

I will not to go into the detail of the numerous elements that need to be considered when developing and implementing a treatment policy, but I would like to give a sense of the complexity and the number of different people involved in the process. A sound legislative and regulatory framework is required, and then there is the issue of selecting which drugs are going to be in the policy, issues of procurement and distribution, the quality of drugs, and the need for countries to develop the capacity for quality control. Good information systems are crucial not only for providing data on which to base a policy, but also to monitor and evaluate the outcomes of a new policy. Linkages between different parts of the health system and decentralising the responsibilities of districts are very important. Financial management is obviously a major consideration. Public awareness and disseminating information on a new policy is essential and is quite a costly business, requiring training of health workers, in both the public and private sectors. Integrated Management of Childhood Illness (IMCI) is having quite an important influence on treatment policy in a number of countries. Negotiations with the drug procurement people must take place to get new drugs onto the essential drugs list. Then there are special conditions like epidemic situations and drugs in pregnancy, which have to be taken into account, as well as the question of unified versus targeted policies for

different groups. If there is a wide variation in levels of resistance in a country - does it make sense to have different policies for different parts of the country or is that logistically too burdensome, especially if drug resistance is developing relatively fast?

Attention also needs to be given to the mechanism of developing the policy process and who should be making the policy decisions. In the end it is a national responsibility, but the dilemmas facing national programme managers are complex and they are increasingly asking for advice and information from outside. Obviously international bodies have a major role in giving advice on treatment policy, and the extent to which guidance can be given to countries is something that needs more action. Regionally, the role of private companies is essential and much work is going on now to give guidance to countries. At country level there are obviously many different players involved in the policy development process.

Some of the major difficulties in setting policy are noted here. Firstly, there is an alarming lack of information. Obviously a policy needs to be as evidence-based as possible, but there are many unanswered questions and gaps in our information, forcing people on occasions to make decisions without enough evidence, because decisions have to be made here and now. Perhaps more thought needs to be given to systematic ways of intensifying the collection of that evidence.

Then the two important goals of the policy, effective treatment on one hand and avoiding the development of drug resistance on the other, suggest in some ways conflicting and different approaches. For convenience, ease of treatment and good compliance rates, a single dose, long half-life drug will often be more practical. In order to avoid the development of resistance, however, short half-life drugs, are preferable and these need longer treatment courses, with associated problems of compliance. Obviously with these conflicts, compromise is needed, slowing down the decision making process. Although there are some effective drugs available, none of them is ideal, and each has disadvantages. The question is how can we speed up the process of making the best drugs available and avoiding unnecessary deaths, and can this be done without unacceptable costs in terms of future resistance development?

Obviously the importance of prolonging the useful life of antimalarials by delaying resistance is clear, but then there is also the question of who benefits from the strategy if the best drugs are limited and used unofficially; limited by their cost only to those who can afford them. By the time they get into public use several years later, resistance is already developing which means that it is not the poorest people who are going to benefit. Anne Mills mentioned earlier that in terms of cost effectiveness at fixed levels of resistance the early change from chloroquine to sulfadoxine-pyrimethamine (SP) is very cost effective. Allowing for changes in resistance may be optimal, but then we can't predict the rates of resistance development.

In the past, the classical sequence for a change in first line drug has been to go from chloroquine to SP, but it might be questioned if this really is the best option. Resistance to SP develops very quickly, as has now been seen in Tanzania and Kenya. SP also produces very high density and prevalences of gametocytes, and the issue of what this may do to transmission rates in areas of lower transmission is worth considering. The use of SP for intermittent presumptive treatment of malaria in pregnant women has shown very good results, prompting the need to consider whether SP should be saved for pregnant women, as there are so few alternatives available.

Issues of cost, cost effectiveness and financing mechanisms are major determining factors. The costs of some of the common antimalarials obviously vary substantially from country to country, but average comparative prices are given here.

Adult dose	**US$ average (1995)**
Chloroquine	0.13
Sulfadoxine-pyrimethamine	0.14
Amodiaquine	0.20
Mefloquine	4.59

Oral quinine	2.68
IV Q 1st dose	0.47
IV Q per day	0.71
Malarone	free/ c.40
LapDap (predicted)	0.25

The cost of changing first line drugs is very high and this may strongly influence how often countries can consider changing policy. This includes the costs of consensus building, dissemination of change, producing guidelines, and adapting supplies, which are very burdensome processes. It was calculated in Malawi for instance, that the process may have cost more than half a million dollars. So it might certainly be questioned whether it is worth going through this change for a drug which is not going to last very long.

Regarding the financing of antimalarial drugs, pharmaceuticals in developing countries consume a very high percentage of the total public and private health spending (estimated between 25-66%) and much lower in richer countries (estimated 10-15%). A strategy to achieve as much equity as possible is therefore required. Different strategies to be considered include public financing, health insurance, user charges, voluntary funding, donor financing and development loans. This needs to be worked out carefully, especially if we are moving towards the use of combination drugs.

The role of the private sector is obviously extremely important, both as a manufacturer and supplier of treatment. Companies have much to offer in terms of favourable pricing structures, provision of expertise and support for local formulation of drugs. Policy makers must take the private sector fully into account and consult with them.

The development of strategies for monitoring and evaluation is another issue. Attempts at the routine monitoring of drug efficacy have only started recently in Africa. There have been many *ad hoc* tests in different locations, but in the last few years, good progress has been made in introducing more standardised approaches, with particular support from AFRO and CDC. Some parts of Africa are better covered by systems of routine monitoring than others. The East African Network for Monitoring Antimalarial Treatment Efficacy (EANMAT) is a very good model that other areas may be interested to emulate. However, the numbers of tests carried out are small and the tests are very labour intensive. More research is needed on monitoring resistance through routine health systems to develop more effective approaches.

Drugs for pregnant women

Pregnant women are evidently one of the most vulnerable groups of malaria patients, but they have the most limited choice of drugs available to them. There have been excellent results from intermittent presumptive treatment with sulfadoxine-pyrimethamine (SP), but once resistance to SP has developed there are very few alternative options. It may also be difficult to justify the cost of introducing a system for provision of SP in pregnancy if the useful life of the drug is very short. Another problem is that not enough is known about the mode of action of the drugs in pregnancy to know the effectiveness of drugs where resistance is already a problem. We do not know much about the effects of short half-life drugs, such a LapDap, in the prevention of malaria in pregnancy, and this may require exploration.

New options

Combinations of standard antimalarials with artemisinin derivatives have been covered very nicely by Nick White in his presentation. Other options for new drugs include coartemether, atovaquone-proguanil (Malarone) and pyronaridine as well as recombination of old drugs e.g. chlorproguanil-dapsone (LapDap).

The principle of combination therapy with artemisinin derivatives certainly makes sense. However, combinations of drugs may only delay resistance in certain circumstances where there is a high level of recombination (Curtis and Otoo, 1986). The potential benefits of the gametocytocidal effects may be very great (Price et al, 1996), but the effects on the gametocytes are not fully understood and not all of them are killed (Targett, 1999).

There are a number of operational issues that need to be considered in combination therapy. Ideally the two components should be in one tablet for compliance and ensuring that *both* parts are taken. However the registration of co-formulated combination drugs is time consuming, and so the sooner this process can start the better. The issue of ensuring that both parts are taken if the two components are not in a single tablet needs urgent research; for example examining the role of blister packs. The question of how universally the combinations need to be applied also needs some thought. And then the cost issues are going to be very important, such as who pays and what will be subsidised?

The new drug Malarone is a very effective 3 day treatment, but difficult to synthesize and very expensive. Glaxo-Wellcome has agreed to donate up to one million doses per year, and the Malarone donation programme is working with the Kenyan Ministry of Health to explore its role for SP failures in two districts. The Malarone donation programme is providing useful lessons on the operation of antimalarial drug donation programmes. For instance, in relation to the costs of adding a new drug to policy and the mechanisms for consultation. Pyronaridine is likely not to be available until 2005. Another promising candidate is LapDap, which hopefully will be available by the year 2002.

Both LapDap and SP are antifolates and there is a potential risk that use of SP may generate parasites that are cross-resistant to LapDap. However, LapDap appears to be effective against at least some types of SP resistant parasites. Amodiaquine could be an interim alternative first line combination with artesunsate instead of SP (Watkins, 1998). This may be advisable, but then the cost advantage would be lost. In view of the length of time it takes for a policy change to be implemented, countries should perhaps be working towards gathering relevant information on the alternative options. These are also systems opportunities for improving treatment policy, as better delivery of drugs would actually make a major improvement in the effectiveness of those drugs.

Conclusions

So to summarise the needs: What is required in developing drug policy is rationality, as much evidence as possible, communication, financial resources, involvement of all key individuals and obviously the development of new drugs. The initiatives that are going on to address these critical issues include capacity development, improved information systems, the use of social marketing of appropriate treatment, and learning from other diseases. The countries themselves are obviously doing a lot, as well as AFRO and other parts of WHO, the East African Network (EANMAT), Medicines for Malaria Venture, donation programmes, research institutions, and funding agencies.

Urgent Next Steps

The situation in East Africa is critical and needs an urgent response. AFRO is in the process of formulating a drug policy framework. This will develop further at a meeting in May 1999 and is a key step in the process of supporting countries. Once there is consensus on the framework, intense activity will be needed in some countries, with external technical support. Funding agencies might consider giving additional resources for relevant data collection and policy development. Generally improving health systems can also have a major impact. And finally there are numerous operational research needs, with an important opportunity for focused research capacity development in African countries. In conclusion, all parties need to think how they can respond to meet the challenge of delivering prompt effective malaria treatment to where it is needed across the African continent.

Country Priorities and Plans for Chemotherapy for Malaria Control in Africa

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Background

The Regional strategies used for control of Malaria in Africa include: case management, vector control and personal protection with emphasis on insecticide treated nets, epidemic preparedness and contrainment as well as operational research to improve the tools that are available. The use of these strategies are dependent on the epidemiology, and human and scientific resource base of each endemic country.

The majority of the African continent is endemic for malaria, with 74% of the population living in highly endemic areas. Therefore, for a long time to come, case management will remain an important strategy for the control of the disease in the African continent. This is because even where there are highly effective vector control programmes, there will still be breakthrough attacks because of low level transmission that will be going on all the time.

In 1994, WHO defined a set of standards for malaria control policies and stated that the primary purpose of effective case management using rational antimalarials is to ensure prompt effective and safe treatment of malaria disease. Effective treatment could however be defined as i) clinical remission, ii) clinical cure and iii) parasitogical cure. For the majority of African countries, the latter goal may be elusive because of the high level of asymptomatic carriers that are already in the population. Therefore, for the primary purpose, an achievable goal would be the clinical cure of the disease. The secondary purpose of rational case management would be to minimise the selection pressure for the development of resistance. Urgent strategies to minimise the appearance of drug resistance to the few effective compounds that are available are needed, if we are not to be confronted with a situation where we would have few options for treatment.

The reasons why chemotherapy or case management has remained one of the important mainstays of malaria control in Africa include the following: it has been found to be cost effective and cheap, and relatively easy to implement on the field in comparison to other strategies. Indeed, the initial capital investment for chemotherapy within a control programme has been demonstrated to be low compared to other measures like vector control. In the long term, the cost to the programme is minimal because the cost is usually borne by the individual patients. The technology associated with case management is not complicated because it involves administration of the drugs concerned, and for the majority of patients, this will be by the oral route. Chemotherapy is usually applicable at different levels of the health care system, and it is not difficult to teach individuals even at the community level how to protect themselves with medicines. Changes in the first line drug does not necessarily mean changes in techniques. With the current on-going health sector reform, chemotherapy appears to be one strategy that can be easily applied even in remote areas, since equity is one of the important goals of health sector reform.

The development of antimalarial drug resistance has however compromised some of the goals and comparative advantages that have been described above. In the field of antimicrobial treatment, resistance has come to stay and will always evolve given time. Therefore, implementors of malaria control should always be one step ahead of the evolution of resistance in their environment. One of the primary strategies that is being employed for chemotherapy is the deployment of rational antimalarial drug policies.

Since 1996, WHO has held a series of meetings in African countries on the problem of rational drug use for the treatment of malaria and the development of antimalarial drug policy. The product that will come out of this cascade of meetings is a rational framework for developing antimalarial drug policies in Africa. This framework has been developed within the concept of health sector reform and the integrated management of disease. This is in line with the

current RBM philosophy which is using malaria to spearhead the management of communicable diseases in Africa.

Principles for Minimising Drug Pressure

We are forever confronted with the prospect of the emergence of drug resistance no matter how low the drug pressure in the field. The rate at which resistance will however appear, will depend on the inherent properties of the drug itself, and the extent of pressure to which it is subjected when in use. There are certain principles which implementors should try to uphold in order to reduce the amount of drug pressure on a compound that is deployed for control purposes:

1. New compounds should as much as possible be deployed only in areas where there is documented need.
2. Use the new compound in combination treatment.
3. Maintain strict compliance with treatment regime (give maximal tolerable doses).
4. Ensure strict follow-up of all cases and vigorously treat all recrudescence with alternative sensitive compound.
5. Vector control measures with special reference to personal protection should be vigorously pursued where a new compound is deployed.

Monitoring Systems

With the spectre of the emergence of antimalarial drug resistance always before us, it is important that monitoring systems should be established in order that susceptibility to antimalarial drug can be detected early and combative measures instituted. There should be a core group of professionals within the national malaria control programmes who have the responsibility of monitoring the emergence of antimalarial resistance. They should work in collaboration with research institutes so that their techniques can be improved in line with more recent research finding. At the present time, because of the poor relationship between in-vitro susceptibility and in-vivo sensitivity, WHO has recommended the use of the in-vivo method. This does not de-emphasize progress to find cheap and rapid ways of detecting and mapping out resistance. Each control programme should have a database on which the scientific and longitudinal perspective of the sensitivity of antimalarials in common use are placed.

In addition to this, there must be a network of sentinel sites in each country to represent the various epidemiological situations that are present in the country. It should be remembered that for large countries, one or two sites would not represent the current sensitivity pattern.

The national health information systems in each country should be strengthened in order to have a reliable reporting system that would flag decreased clinical usefulness of a drug and possibly be a herald for formal sensitivity studies. The importance of such a reporting system cannot be overemphasized. Indeed, such a system might be the first indication of a much bigger problem. These monitoring systems should be initial data to signal that a change in treatment guidelines may be required.

Framework for Antimalarial Drug Policy

Although many African countries have always had vector borne disease control units which are responsibility for malaria control, it was peculiar that, despite the fact that it was known that the mortality and morbidity from malaria was very high, very few African countries had antimalarial treatment guidelines or even had control policies at the beginning of the eighties. This was not unconnected with the fact that the operational research needed to gather the data required for developing these guidelines were usually contracted to bodies other than the Ministries of Health which had the mandate to develop and revise guidelines.

One of the aspects that the Malaria Control Programme at AFRO has developed, is capacity building in some areas that are important for the development of antimalarial drug policies. Specifically, capacity has been built in 31 countries of the continent in therapeutic efficacy test. In addition to this, WHO has produced guidelines for carrying out these studies at the

district level. In these countries, sentinel sites have been set up so that each country could have data bases that would provide scientific longitudinal perspectives of the problem of sensitivity to the commonly utilised antimalarials in the individual countries.

WHO has gathered experience in assisting countries with the provision of rational malaria treatment guidelines. In the first place, there must be evidence for the update of a policy. This will be in the form of formal efficacy studies, studies on the efficacy of the putative first line drug, with data on the economic advantages of changing from the current first line drug. At the time when the treatment guidelines are being changed, the policy makers should be very careful to make sure there is participation of all the stakeholders that are involved in the process. One of the ways in which this can be achieved is to set up a multi-disciplinary body to supervise the implementation of the process. At this stage, indicators for monitoring and evaluation of the process should be developed so that instruments for constant monitoring and evaluation may be put in place. Operational research issues will be one of the priorities of this multi-disciplinary body to ensure that operational questions are answered as the process goes on.

Operational Research for Combination Therapy

As policies are updated or changed, depending on the circumstance of each country, the options that are open for case management of the uncomplicated disease will diminish. Unfortunately, in the field of malaria chemotherapy, there are few options open as substitute for the currently used first-line antimalarial drugs. There is wide-spread chloroquine resistance, and increasing resistance to sulfadoxine pyrimethamine which is the drug that many countries are hoping will replace chloroquine.

Since combination therapy is a well known strategy to slow down the emergence of resistance to an antimicrobial compound, there is much interest in the development of rational combination treatment regimes using different principles to slow down the emergence of drug resistance. This is an area of great focus for the TDR. At the present time, a region wide combination trial of various compounds with the artemisinin compounds are going on in order to obtain a “proof of principle” for combination therapy in areas of intense transmission. Following these series of investigations, the studies will be done to find out the effect of wide scale use under implementation and control conditions on 1) rate of emergence of resistance, if at all and 2) the effect of the combination on the burden of disease.

These are very exciting and promising times in the various studies that are going on in relation to chemotherapy in the continent. One aspect that is obvious would be how to accommodate the rapidly changing scenario within the concept of a rational antimalarial drug policy for the countries of the region.

Approaches to Chemotherapy

Several opportunities have opened up for the effective implementation of case management of malaria at different levels of the health care system. One of the most important opportunities for case management of malaria for children five years and below is the IMCI approach. Within the region, more than 20 countries have now adopted the IMCI approach to the management of febrile diseases. A recent monitoring visit to Tanzania by a joint WHO/DFID team demonstrated that the IMCI approach improved the skill of health care personnel trained in case management. It also showed an increase in the number of attendances at health care centres due to improvements in disease management and relations with the consumers. Many countries within the region are making the approach a priority programme to tackle the menace of high childhood mortality and morbidity. It is expected that, as new tools for example combination therapy for the treatment of malaria disease come up, they will be incorporated into the IMCI approach.

The IMCI approach has three aspects. First is case management which has a syndromic approach. By rational utilisation of common symptoms and signs, putative diagnosis of the common febrile illness are made. Management is then carried out within the limits of the

national guidelines for the particular illness. Follow-up and counselling are important aspects of case management using the IMCI approach. With over 40% of childhood fevers being attributed to malaria in endemic areas, the importance of the IMCI approach for the management of malaria cannot be overestimated.

The second aspect of the IMCI approach that is very important to case management is community management of disease. It is known that the majority of deaths in the Region take place at the community level. Therefore, by utilising this approach in IMCI, it is expected that the philosophy of early diagnosis and prompt treatment of illness will be better realised. Finally, IMCI aims to use its approach to tackle the problem of health systems. IMCI will address the issues of costs of implementation, the drug supply management organisation of work at the health facility level, problems with support systems and the problem of referral.

The last aspect of IMCI is the question of the approach and how it will influence health systems. This is important, as challenging changes are taking place in our health systems in the continent with cost of the approach, sustainability, user fees, and referrals being aspects that the IMCI approach expects to positively influence. We can therefore see that the IMCI package has a lot to offer in terms of case management for children under the age of five years.

The malaria programme itself has adopted as one of it major strategies, community management of the disease. The thrust of this strategy is to use workers within the communities to make rational decisions on the drug treatment of fevers in all age groups, whilst ensuring that the commonly used first line drugs are available. Referral systems will be examined for each situation. This approach would, in the long run, assist with the much-needed reduction in mortality from malaria in the region where it is effectively carried out. The catchment population for each community is all persons that are at risk for malaria disease.

Since women in the reproductive age group form a significant proportion of the population in the continent, and pregnant women are more prone to developing problems associated with malaria disease, the reproductive health programme will be one channel that would be used to ensure that women in the child bearing age group are catered for. In addition to this, the region is in the process of re-evaluating its policy for prophylaxis and the management of malaria in pregnant women. This would not be an easy task in the face of rising antimalarial drug resistance, dwindling resources, poverty and inequity in the region, especially in this instance with respect to women.

Implementation Challenges

The operational challenges to case management will become more difficult with the passage of time. The experience in the region has been that there is no easy path to updating policies, because they affect people and society. As we change first-line drugs, the cost to the programme will have to be carefully evaluated. This is because all the proposed new compounds are multiples of the cost of chloroquine, which is arguably currently the cheapest antimalarial. In the final analysis, the cost of treatment will be mostly borne by the patient, which may further aggravate the problem of inequity. A situation where only a small segment of the society is able to afford antimalarial drugs should not be encouraged as the disease knows no boundaries.

Changes in drug treatment are often accompanied by the problems of acceptability of the new regime. Changes from Chloroquine to SP have often been resisted on the part of the providers and consumers who may feel that SP is an “inferior” drug. The social perspectives of all antimalarial drug treatments have to be carefully managed. Compliance to the new regime may not be fully divorced from social acceptability. This is because where the regime for treatment is difficult to follow, there would be problems with drug pressure. Where two or even three compounds are required, then the problem of compliance would be even further exaggerated.

It is important that as we move from mono-therapy to combination therapy, the mode of delivery of the drug should be simple. This is more important for delivery through infusions in the case of severe disease. Where the delivery mode is not simple, it is not likely that the new regime will be rationally used in the peripheral area where the majority of the population live with grave consequences for the development

The question that always confronts implementors are these: will the drug reach the majority of the people; will they be able to afford it; how soon will resistance appear; and if resistance does appears, is there an alternative? These are not easy questions to answer.

Collaboration

Successful implementation of the malaria control strategy in the region will depend on a number of factors, an important one being collaboration with partners. These partners are themselves implementors. Therefore, WHO should be a brokering partner to ensure that partners follow national antimalarial drug policies. Where policies are not adhered to, a chaotic situation emerges which introduces complex drug pressures on the field with totally unpredictable results. The few antimalarial compounds that we have are so precious to us, that all partners should collaborate to avoid the situation where a chaotic scenario emerges.

Industry has often been ignored in the process of developing drug policies and treatment guidelines. The complex situation of emerging resistance makes it imperative to involve industry early in the process of change. Industry has a lot to offer in the areas of costing, packaging and fundamental research that may restructure the whole way in which we perceive case management.

Concluding remarks

The importance of chemotherapy to malaria control programmes will continue to increase, bearing in mind the epidemiology of the disease and the increase in the spread of malaria in the African Region. New approaches to case management in the African Region have to be opened up if we are to meet the current challenges that face us in this Region. New research to find drugs, either singly or in combination, that may reduce the burden of disease, are currently needed. This of course will be in addition to the use of other techniques such as personal protection and vector control. It is a combination of various strategies that will ultimately reduce the high mortality in the short- and medium-term, and high morbidity in the long-term, that have for so long been the scourge of malaria in the African Region.

Collaborations to Address the Challenge of Antimalarial Drug Resistance

Peter Bloland, Centers for Disease Control and Prevention, Atlanta, USA

The last few years have produced a significant surge in interest, energy and resources aimed at malaria. Along with this increased interest and enthusiasm, there has been increased recognition of the benefits of broad collaboration and willingness to enter into collaborations with a variety of new or nontraditional partners. Collaboration has played a key role in the area of antimalarial drug resistance in the past and will be essential to effectively meeting this growing challenge in the future.

For the next few minutes, I would like to talk about three truly multilateral collaborations that CDC has had the pleasure to participate in, two that have been ongoing for a few years, and a third that is just beginning to be put into place.

One of the interesting characteristics of all of these activities is that the involved partners did not necessarily start out with the intent to collaborate, but rather they came together through a realisation that the scope and nature of the problem of drug resistance was such that no single group could succeed on its own, a recognition that others shared their goal and commitment, and an acknowledgement that each group had something unique and important to contribute to the effort.

The first was an effort that brought together components of WHO, CDC, USAID and a number of ministries of health and medical research institutes in Africa, to develop a standardised protocol for assessing antimalarial treatment *in vivo.*

Granted, this was not a new concept. Standardised protocols had been developed in the past and the fact that nearly everyone in this room can recite the definition of RI, RII, and RIII attests to the wide spread use of these protocols over the years.

Reviewing reports of studies using these standardised methods published over the last 10 years, a picture can be generated that illustrates the status of antimalarial drug resistance in Africa. But, unfortunately, it is not a picture without significant problems.

The first major problem is a methodological one: the extent to which, over the years, this methodology has been modified. Modifications have been so extensive and so different between researchers, sites, and years that it is not unusual to find two separate evaluations of the same drug conducted in the same area during the same year that yield results that support dramatically different and conflicting interpretations.

The second major problem is a functional one: the results of studies using this methodology have not been highly successful in motivating change in malaria treatment practices in Africa. There are many reasons for this, but one of the most important reasons is that while these methods gave reasonable data about how healthy parasites respond to antimalarial drugs, they gave little information about how sick people respond to malaria treatment. This limited the potential programmatic impact of the data collected over the years. So while an interesting picture can be made, it is difficult to know what to make of the interesting picture.

The goals that have developed within this collaboration were:
First, to design a programmatic tool for collecting highly comparable information on the current efficacy of malaria treatment options across the region, and second, to allow more reliable comparisons of information across time and geography. To do this successfully, the new protocol needed to have outcomes that reflected and focused on patient responses to treatment, to be relatively simple in design so that people not coming from a research background could easily be trained in the methods, and to be sustainable in terms of the time and resource investments required.

The result of this collaboration is a protocol that goes a long way towards fulfilling these objectives. WHO-AFRO, a critical partner in the development of the protocol, has since been exceedingly busy in training control programs in the methodology and supporting its use throughout Africa.

The early results of these efforts are promising in terms of the amount of highly comparable data collected in a short period of time. Again, one can begin to piece together a picture of the current status of malaria treatment in Africa, but with a major difference. This time, because a truly standardised methodology was used throughout, the picture is one that we can easily interpret and use with confidence. Over time, provided these methods can withstand people's natural inclination to modify, this picture will become more detailed.

But collecting data on response to antimalarial treatment is not an end in and of itself. To be useful, information must be used. Once again, a collaborative effort developed out of a shared recognition of need. Many of the collaborators who worked together on the standardised protocol were joined by new partners, notably DfID and the Wellcome Trust, in investigating how information is used in antimalarial drug use policy development and decision making.

There were three primary observations that drove this collaborative effort.

1. It became apparent that antimalarial treatment recommendations lagged behind the actual status of antimalarial drug resistance.
2. Parasitologic resistance data and biomedical arguments for policy change alone did not appear to be sufficient evidence in the eyes of decision-makers to warrant major policy change.
3. Although we knew quite a lot about those biomedical arguments, collectively we know little about other influences on the process of policy-level decision making or about the process of decision-making itself.

The general goals of this collaboration were:

- To elucidate the relevant inputs that go into the process of developing policies that seek to address drug resistance and malaria therapy;
- To encourage more active participation of representatives of other disciplines in the policy dialogue especially behavioural scientists, economists, and the private sector;
- To improve the understanding of the decision making process itself; and
- To utilise this information to improve countries' ability to effectively address the challenge of antimalarial drug resistance as well as to improve the international community's ability to assist and support this process.

Towards these ends, a number of agencies co-sponsored a series of workshops on antimalarial drug use policy development that included over 60 participants from 23 countries. An important aspect was the inclusion of representatives from both the research community *and* the programmatic community.

The objectives of these workshops were to discuss options and approaches to meeting the challenge of drug resistance in Africa, and equally important, to identify and discuss important inputs to the process of developing proactive drug use policies.

In additional to the biomedical inputs so frequently and extensively investigated in the past, the other important inputs identified and discussed at these workshops included:

- Epidemiologic inputs - especially regarding the public health impact of resistance such as has been discussed earlier by Jean-Francois Trape;
- Socio-behavioural inputs - issues like treatment seeking behaviour, acceptance of policies and treatments, and compliance with recommendations not only on the part of patients, but also on the part of providers;
- Political inputs - from the level of political will within a given country to the complex interrelationships between public health and other important public policy components;
- Economic inputs - including costs and cost-benefits;

- Legal-regulatory inputs - including how new drugs are introduced into a country and what countries can do to encourage appropriate use though regulatory systems;
- A large group of cross-cutting issues including the role and influence of international pharmaceutical companies and the local private sector.

These workshops were merely one step in a long process, but highlighted the fact that, without a level of attention and understanding of these inputs equal to what we have applied to understanding how parasites respond to drugs, moving towards the ultimate goal of improved case management and limitation of the impact of drug resistance will be difficult, if not impossible.

Now that we have what we hope is a useful and useable method for assessing antimalarial treatment efficacy as well as an improving understanding of how to use this and other information to develop policies and practices to address the threat and reality of drug resistance, many have recognised a need to monitor changes in drug resistance and hopefully, the impact of drug use policies on the spread and intensification of resistance across the region.

To do this, another collaborative effort is proposing to create a surveillance system for tracking changes in antimalarial drug resistance in Africa. Although specific contributors to this effort can be identified as I have attempted to do here, the ultimate success of this proposed collaboration really rests on the participation of everyone in Africa involved in antimalarial drug efficacy testing. This will truly need to be a region-wide, all-inclusive collaboration.

The goals of this proposed collaboration are:

- To create a unified, single source surveillance system for drug efficacy data for all of Africa;
- To tract temporal and geographic trends and to link these data to other available malaria data;
- To make these data readily available to all who need or have an interest in them; and
- To use this activity to continue to build capacity of participant institutions and individuals in Geographic Information Systems, efficacy testing and surveillance methodology.

To do this, the partners are proposing to build on the existing infrastructure and methodology of the MARA project to create a “network of networks” with all those who are engaged in efficacy monitoring. In order to return the information collected to all who wish to use it, we are proposing to develop information dissemination systems that also build on existing resources as well as to provide reports on antimalarial drug resistance tailored to specific uses, countries, sub-regions, and Africa as a whole.

In conclusion, while there are certainly many more collaborative efforts that have been or will be discussed during this meeting, these few examples illustrate how, working together, significant contributions to the fight against antimalarial drug resistance can be made. The enthusiasm and interest in developing new collaborations to address specific issues in malaria and the willingness to welcome new voices and opinions into the effort is exciting, and I think we all look forward to hearing about their successes in the future.

BREAKOUT SESSIONS: ANTI MALARIAL DRUGS

Programme

1. Meeting Challenges with Antimalarial Drugs in Africa.
Chair: Dr. Don Krogstad and Professor Ayoade Oduola
Rapporteur: Olumide Ogundahunsi, A. Akanmori, Catherine Falade

Presentations (15 mins each)
1. Needs and priorities for effective utilisation of antimalarial drugs in Africa - Tom Sukwa.
2. Process and Implications of Drug Policy Change for Malaria Control.
   - Malawi experience - Peter Kazembe.
   - Kenya experience - Beth Rapouda.
3. Integrating *in vitro* and *in vivo* Drug Sensitivity Monitoring in Malaria Control: Experience.from Mali -
   Ogobara Doumbo and Chris Plowe.

Abstract Presentations (5 mins each)
1. Molecular epidemiology of drug resistance: Suitability of assays for surveillance under the MIM network in Africa - Chris Plowe.
2. Needs assessment for the development of drug policy for front line health workers - Amos Odhacha.
3. Establishing malaria treatment policies in Burundese refugee camps in western Tanzania 1998 - Holly Ann Williams.
4. Monitoring the efficacy of sulphadoxine/pyrimethamine in falciparum malaria around Muheza, Northeast Tanzania - Martha Lemnge.

Discussion 15 minutes

2. African Scientists and Institutions in Developing Drugs for Malaria.
Chairs: Dr. Wilbur Milhous and Dr. John La Montagne.
Rapporteurs: Christian Happi, Grace Gbotosho, Wilfred Mbacham

Presentations
1. Drug development Needs and Resources - Dennis Kyle (20 mins).
2. Drug Registration Policy - Peter Folbe.
   New Initiatives for Malaria Drug Discovery
3. New Medicines for Malaria Venture - Rob Ridley (15 mins)
4. Harvard Malaria Initiative - Dyann Wirth (10 mins)
5. An overview of Potentials and Resources available in Africa - Bill Watkins (10 mins).

Panel Discussion: Perspective on Political, Practical and Economic Implications of Integrating African Scientists and Institutions in drug development for Malaria.
Moderator: Dr. Rob Ridley
Rapporteurs: Dr Wilfred Mbacham, Dr. Grace Gbotosho and Dr. Stephanie James
Panel: Dr. Bill Watkins, Dr. Dennis Kyle, Dr. Carlos Morel, Professor Dyann Wirth (5min), Dr. John Horton (5min), Dr Michael Gottlieb.

3. Joint Session: Management of Severe Malaria and Antimalarial Drugs
Chair: Dr. Pascal Ringwald and Dr. Piero Olliaro
Rapporteur: Dr. Didier Diallo, Dr. Dora Akinboye, Dr. Eric Achidi

Presentations (20 mins)
1. Implications of drug resistance and loading dose in treatment of severe malaria in Africa - Akintunde Sowunmi.
2. Current practices and Potential Role of antimalarial suppositories in management of severe Malaria in Rural Areas - Melba Gomes.
3. Meta-Analysis of arthemether and quinine trials in management of severe malaria - Nick White.

Abstracts (5 min each)
1. La quinine en solution intrarectale est efficace dans le neuropaludisme et les acces graves de l'enfant en Afrique - Hubert Barennes.
2. Artesunate suppositories in the treatment of moderately severe malaria in Malawian children - Madalitso Tembo.
3. A randomised, placebo controlled, double-blind study of the tolerability and efficacy of Artesunate plus sulphadoxine/pyrimethamine combinations vs. Single-agent sulphadoxine/pyrimethamine for the treatment of uncomplicated falciparum malaria - Lorenz von Seidlein.
4. Comparative efficacy of chloroquine and co-trimoxazole in acute uncomplicated falciparum malaria in children - Adegoke Falade.

Summary Report: Antimalarial Drugs

Management of Severe Malaria and Anti-Malaria Drugs – Joint Session

Chair - Dr Piero Olliaro
Rapporteurs: Drs D. Diallo, D. Akinboye and W. Mbacham

Research priorities

- Investigate unmet applications of new drug formulations to reduce evolution to and mortality due to severe malaria.
- For uncomplicated malaria, the identification of effective drug combinations which may delay or reduce the establishment of drug resistance.

Implications of Results for Control

Artemether-Quinine Meta-analysis study

- Artemisinin derivatives are still the most rapidly acting anti-malarials
- A meta-analysis study in both adults and children of 7 randomized trials in severe malaria show that Artemether tended to achieve more rapid parasite clearance and was significantly better in some subset analyses but overall, was not significantly better than quinine in reducing severe malaria mortality.
- A significant improvement in terms of lives saved cannot be expected in Africa upon introducing Artemisinin-type compounds based on available evidence and current quinine efficacy. However, these results show that Artemeter can be expected to be as good as quinine and potentially better in case of quinine resistance. A reduction in mortality should then rather be sought in earlier, nearer-home interventions

Alternative Forms of Drug Administration

- Intra-rectal use of quinine solution was effective in children with moderate neurological symptoms and in severe malaria, and may serve as an alternative for intra-muscular or infusion quinine treatment especially when a child has not got diarrhea. Further research is needed on formulations.
- Rectal Artesunate was effective for emergency treatment of moderately severe malaria with reduction in parasite density and fever. Single dose rectal Artesunate must be followed by an effective parenteral or oral treatment. A dossier for registration will be submitted by the WHO soon.

Multi-drug Therapy

- **Chloroquine and Co-trimoxazole** in acute uncomplicated *falciparum* malaria in children, in Nigeria were equally effective individually in reduction of fever and parasite clearance time. No difference was found between 3-day and 5-day treatment courses with Co-trimoxazole. While this could offer options for treatment, of children with overlapping symptoms of malaria and respiratory infections, the implications in terms of parasite and bacterial resistance generation are not known

- A combination of **Fansidar and Artesunate** (1 and 3 doses) resulted in faster parasite clearance and faster disappearance of gametocytes with respect to Fansidar administered alone. Gametocytes were still infective in mosquitoes 4-7 days post-treatment. The problem that remains to be solved is to investigate the difference between gametocyte persistence upon treatment with Fansidar and the Fansidar-Artesunate drug combination. This was one of a series of multi-center studies due to enroll several thousands patients across Africa.

- Examples of combination of **Chloroquine and Resistance Modifiers** requires multiple administration over seven days. Though impractical, they represent a “proof of concept” that resistance can be reversed *in vivo*.

MANAGEMENT OF SEVERE MALARIA

Plenary Presentations

Overview of Clinical Malaria in Africa
Cathy Waruiru

Management of Severe Malaria - Implications for Research
Kevin Marsh

Breakout Sessions

Programme

1. Joint Session: Management of Severe Malaria (I) and Antimalarial Drugs
2. Management of Severe Malaria: Session II
3. Management of Severe Malaria: Session III

Summary Report

PLENARY PRESENTATIONS

Overview of Clinical Malaria in Africa

Cathy Waruiru, Wellcome Trust-KEMRI Collaborative Research Programme, Kenya Medical Research Institute, Kilifi, Kenya

If one goes to practically any hospital in large areas of Sub-Saharan Africa and asks - What is the commonest disease? Or what is the biggest problem? The answer will invariably be "malaria".

Data collected in the early, descriptive stages of a series of studies carried out in collaboration between the Kenya Medical Research Institution and the Wellcome Trust at Kilifi shows the relative importance of malaria as a cause of death in inpatients in Kilifi hospital on the coast of Kenya.

Despite over 100 years of scientific investigation, there has been relatively little empirical description of the disease particularly among children, who take the brunt of *Plasmodium falciparum* infection. This has changed over the last decade or so, during which time a number of groups throughout Africa, all of which are represented at this Congress, have gradually built a fairly comprehensive picture of the clinical and epidemiological features of the disease. During this talk I will attempt to provide an overview of our current understanding of severe malaria in African children and to draw some attention to some of the new insights that have emerged.

Why is it necessary to understand the underlying disease processes rather than take the simplistic view that all that is needed is an adequate supply of anti-malarials?.

The majority of children who die do so within the first 24 hours (up to 80%) and many within 12 hours. Even the most effective antimalarials are unlikely to abort the progression of disease at this stage, and reduction of case fatality is likely to depend on building up a clear understanding of the pathophysiological processes at work and developing appropriate therapeutic approaches.

You cannot broach the problem without definitions. Hence in the early 90's a working party of experts developed for WHO such a definition. The point of presenting it at this stage is simply to illustrate the fact that it is a complex definition based on a mixture of clinical and laboratory observations, some of which cannot be made in the average hospital where malaria is a problem. Note too that this definition was not the result of an empirical study but represents expert views, derived mainly from experiences of non-immune adults from South East Asia. This is not to detract from its value. Indeed this kind of definition is essential for detailed research studies and is being revised. However, a simpler definition or classification would be more useful for many clinical and epidemiological purposes.

At Kilifi district hospital we have tried to develop a simplified way of looking at the clinical spectrum of severe malaria. By examining about 1800 consecutive admissions to the paediatric ward with a primary diagnosis of malaria. Admission policy was determined by ministry of health clinical officers not connected with the research unit. Thus this probably captures reasonably well the spectrum of disease admitted to many such hospitals.

A couple of points deserve emphasis:
The first is that three clinical syndromes account for the majority of deaths - Impaired consciousness (coma), anaemia and respiratory distress. I will elaborate later on what these syndromes comprise.

The second is that, although severe anaemia accounted for the largest group in terms of numbers, the actual case fatality is those who did not overlap with the other groups was relatively low (1.3%).

Finally, and worth our attention, is that from the point of view of severity as defined by outcome, children who present with an overlap of the syndromes, especially that between coma and respiratory distress, have a very high case fatality.

Thus the complexity of severe malaria is this setting can usefully be simplified into three overlapping but reasonably distinct clinical syndromes.

First, **severe malarial anaemia in isolation** , that is when a child is asymptomatic, it is numerically common but with a relatively low case fatality rate, requiring in most cases conservative management and not necessarily blood transfusion.

It is arbitrarily defined as a haemoglobin of less than 5 grms in a patient with a parasitaemia in excess of 10,000 trophozoites per cubic millimeter, with normocytic indices. The problem with such a definition is that parasitisation is common in malaria endemic communities and anaemia is multifactorial, - so that the occurrence of both does not necessarily mean cause and effect. However, it is striking that the incidence of the syndrome, even when defined in this way, closely parallels the incidence of other forms of severe malaria in areas where there is distinct seasonality.

It is predominantly a manifestation of disease in young children (less than 2 years) and we shall refer back to this when discussing some aspects of differences in disease patters in relation to transmission intensity.

Children with severe anaemia who present in respiratory distress and or impaired consciousness are along a more critical spectrum of disease.

Which leads us on to discuss **respiratory distress** . Surprisingly, respiratory disease does not feature in textbook descriptions of severe malaria, yet it is in this group of children that the case fatality is in fact highest. There are many reasons why a child with severe malaria might have respiratory distress. I am going to summarise much research by saying that in the majority of cases respiratory distress is the clinical manifestation of a severe metabolic acidosis.

A total of 238 consecutive children with severe malaria were grouped into i.) no respiratory distress, ii.) respiratory distress, but survived, and iii.)a respiratory disease and death. The degree of metabolic acidosis is measured by the base excess, given as a negative value. Normally, the concentration of hydrogen ions is maintained in very tight bounds by homeostatic mechanisms and the normal base excess is +/- 4. It can be seen that a metabolic acidosis is a common feature of severe malaria and that in children in respiratory distress it is very severe, and even more so in those who die. The underlying reasons why children with severe malaria develop a metabolic acidosis may be complex, but two factors dominate: hypovolaemia from dehydration and severe anaemia, resulting in reduced oxygen-carrying capacity to tissues. This has a number of important implications for the management of severe malaria in children which will be outlined in the next talk, and detailed discussion will take place in the breakout session.

I want to turn now to **coma** , which for the purposes of this presentation, may be taken to be synonymous with the generally used term "**cerebral malaria** ". The classical understanding of cerebral malaria, and one which still seems to underpin quite a lot of thinking and *in vitro* experiments relating to pathogenesis, is based on the histopathological picture illustrated here.

In post mortem samples you can see cerebral vessels packed with sequestered red cells containing mature parasites. When one sees this appearance in the brain of someone who died having presented in coma, it is perhaps a natural conclusion to regard the microvascular

obstruction as the defining feature of the clinical syndrome. However, emerging experience from a number of clinical studies suggests that this is an incomplete picture and that cerebral malaria is not a homogenous condition but a collection of syndromes where different pathophysiological events end up in the same clinical manifestation - coma.

Drawing out these distinctions is important because they have implications for both the management of children with cerebral malaria and for those trying to understand the detailed pathogenesis.

I want to illustrate the four distinct scenarios which converge to produce the same apparent syndrome of which should be familiar to anyone managing children with cerebral malaria.

The first child presents with a history of seizures, possibly one but more typically several, prior to admission to hospital in coma. The child may in addition have few or none of the known poor prognostic factors - such as hypoglycaemia or acidosis. Treatment will usually be initiated with parenteral anti malarials and maintenance fluids. Recovery of consciousness is fairly rapid occurring within 8 hours. It appears that in these children coma is due to an abnormally prolonged post-ictal state. The reasons for this are not yet clear, and though *Plasmodium falciparum* does appear to be epileptogenic, it is difficult to believe that this short-lived syndrome is caused by the classical histophathological picture seen earlier.

The second child may or may not have a history preceding the seizures, but is also brought to hospital in coma. On careful examination, the child may be noted to have one or more of several subtle signs - including irregular breathing (these children often are markedly hypoxic), increased salivation, or nystagmoid eye movements. Cerebral function monitoring or EEG, which is of course not possible in any but the most specialised units, shows that these children are in covert status epilipticus. When given anti-epileptics, they usually recover consciousness over few hours, sometimes with startling rapidity. In a busy hospital ward, these subtle signs may be overlooked as the child is considered to have cerebral malaria. The natural history of this syndrome if not aborted with antiepileptics is not know and one can imagine death ensuring from hypoxia without house in attendance being award that a simple and easily available manoeuvre could make a dramatic difference. Though we do not understand the trigger for the status it is again difficult to reconcile the rapid recovery of this syndrome with the pathology considered typical of cerebral malaria.

The third child presenting in coma may or may not have seizures but on admission, is noted to be having deep breathing - kussmuauls breathing. Where facilities exist, blood gas measurements will show the child to be markedly acidotic. In addition, the haemoglobin may be low, the blood glucose subnormal, and the electrolyte profile abnormal. If vigorous attention is given to the metabolic derangement, the child may again recover consciousness over a few hours. The coma seems to be possibly a protective response to metabolic stress which, when received, results in normal function.

You may by now be wondering whether there is such a thing as cerebral malaria, as typically understood - that is, a primary neurological condition lesion where the primary neurological condition lesion where the primary pathology is in the brain.

The fourth child is one who presents in coma, with or without any of the complications mentioned in the other three scenarios. Despite appropriate management, coma persists for a longer period, between 24-72 hours and, although many recover fully, there is a significant incidence of neurological sequelae, perhaps not when one sees the kind of damage that can be done. A CT scan of such a child, taken some months later, shows extensive brain atrophy.

I hope I have illustrated that a clinical syndrome previously considered a single entity, when subjected to clinical research, actually is more complex. That this complexity is not only relevant from the point of view of management, but also in the attempt to unravel the pathogenesis, the differences are worth bearing in mind.

Up to this point I have attempted to provide an overview of the clinical spectrum of severe malaria in African children. The data has been derived mostly from a specific research unit in Kilifi where I have been involved in clinical studies for a number of years. Similarities emerge in an increasing number of studies from different settings across Africa. But it would be incomplete in a discussion of the clinical spectrum of severe malaria, not to mention some variations in the clinical picture under different transmission conditions. Many of you will be aware that the whole issue of differences in morbidity and mortality with differing levels of transmission has been an extremely contentious issue over the last few years. I have no intention of straying into this debate as the main protagonists are here at this congress and I will have to leave it to them to argue it out. However, there are probably some reasonably uncontroversial points relevant to this discussion.

We have compared the age distribution of children admitted to hospital with malaria in two differing transmission settings - Kilifi, an area of moderate transmission, and Ifakara in Tanzania, an area with considerably higher transmission. The striking observation is that in Ifakara, the concentration of disease is in very young children and consistent with the earlier age distribution profile of severe disease, there is a relatively higher proportion of severe malarial anaemia in Ifakara compared to Kilifi. Where transmission is high, as in Ifakara, children on average will encounter malaria at an earlier age, compared with children in a lower transmission setting.

Interesting data comes from comparing the relative amounts of severe anaemia and cerebral malaria reported in a number of clinical descriptive studies from different sites over Africa. The sites are arranged from left to right in order of increasing transmission density. From Dakar in Senegal, with the lowest level of transmission compatible with stable endemicity, to the very high transmission levels seen around Lake Victoria in Kenya. The relationship is not absolute but this data does show that, whilst the clinical spectrum I have described may be generalised, one can expect local differences in the relative importance of a given syndrome.

In this talk, I began with a useful but complex definition of severe malaria. I moved on to a simpler one based on three main clinical syndromes. There are a number of important pathophysiological processes such as hypoglycaemia and impaired renal function that I have not addressed because their impact is captured in the broader approach we have taken.

I want to finish by emphasising the importance of bed side clinical signs. We have examined the ability of various diagnostic groupings to identify those at risk of dying. The combination of two signs - prostration (inability to sit or feed) and any degree of respiratory distress - forms a clinically useful classification.

For those of us who find themselves faced with yet another season of malaria, at a busy rural hospital, with minimal facilities - this is a practical classification that identifies the children who need attention. The critical signs to identify those requiring attention are prostration or respiratory distress. Clearly, prostration will include all children in coma as well as quite a number with lesser degrees of impairment. The presence of signs often considered to be of major importance - severe anaemia or seizures - do not, on the basis of what now amounts to experience in managing thousands of children, constitute a high risk per se. But because a minority will deteriorate, they too need to be managed in hospital. Children lacking in any of these signs may safely be managed as outpatients.

In closing, although we have concentrated on malaria, in practice, children do not present at health facilities so neatly labelled. But this kind of approach can, with minimal modification fit the integrated management of childhood illness approach.

Management of Severe Malaria - Implications for Research

Kevin Marsh, Wellcome Trust-KEMRI Collaborative Research Programme, Kenya Medical Research Institute, Kilifi, Kenya

Introduction

It is tempting, following a talk that beautifully summarises recent clinical research on malaria, to move straight on to look in more detail at some of the emerging data on severe malaria and to consider what are the potential priorities for clinical research. But particularly in this unique meeting, it is important to take a step back and look at the overall context in which clinical research takes place. Therefore in the next few minutes, I will first briefly consider the process and requirements for clinical research. I will then, in the second half of my talk, review some of the areas where research could make a difference. While I am doing this, I will also flag up areas which will be considered in more depth at the breakaway sessions of this congress.

What's happening now?

The first thing to say is that research on severe malaria is research on failure- failure to prevent malaria and failure to treat it quickly and appropriately when it occurs, well before a hospital is required. In view of this, I am in no doubt that the *fundamental* research priority lies in these areas. Why then do we continue to do research on severe malaria at all? The answer is that even if the most optimistic targets of us all are met, it is still the fact that a very large part of the clinical load facing health care professionals throughout Africa for the next twenty years (at least) will continue to be severe malaria. That being the case, it is very sobering to reflect on how much clinical research has had any real effect on practice in the ordinary hospitals all over Africa that deal with severe malaria on a day to day basis.

Have there really been any major improvements in the past ten, or even twenty years? I wonder how many of us even know what is really going on in these hospitals - what is the case fatality of severe malaria in ordinary, non-research hospitals across Africa? And yet, unless we know what is going on, and probably more importantly what is not happening, we start from a pretty unrealistic position if we want our research to have a real impact. In saying this, I do not simply mean what is happening in technical terms e.g. Can blood sugar be measured? What is the fluid policy? But what is happening in terms of staffing, morale, training and all the other things that have an impact on the care of severely ill children? Of course, one of reasons why we often don't have a clear picture is that this kind of research, whether one calls it audit or operational research or applied health systems research, is very difficult. Unfortunately, it is also seriously unattractive: there are not many papers in Nature or the New England Journal to be had from it. This has to change, or otherwise we really have no basis on which to develop strategies for clinical research which stand a chance of affecting practice.

Research Requirements

Once one knows what is happening, the second requirement is to have a good research infrastructure to generate ideas and act as a test bed to establish which ones are promising - and it is perhaps worth saying a few words about this. The issue of *sustainable* funding for research centres in Africa has already been dealt with extensively, indeed it is part of the whole rationale for this meeting, but it won't hurt to say again that this is an absolute requirement. Related, and as important, is the issue of developing critical mass. This is important for capacity building, but also for raising the intellectual temperature and rigour. No area of science can afford to be happy with just ticking over, but given the scale of the problem we deal with, we more than most simply cannot afford to be carrying out poorly thought-out studies, or rediscovering wheels. With the best will in the world, it really is very difficult to see how much progress can be made by isolated researchers in small groups with precarious funding.

A further requirement is that research at this stage is closely tied in with ministries of health and the national control programmes. There needs to be a degree of involvement or ownership. If this is not established it will be an uphill task to promote policy changes further

down the line. In saying this I am not advocating a prescriptive attitude: to my mind the tension between so called "directed" research and "imaginative" or curiosity driven research is meaningless. What is important is to have short-, medium- and long-term strategies, and to know which is which. Short-term strategies will necessarily be more concerned with immediate realities, while long-term strategies may involve a large degree of speculation, the applicability of which may not be immediately apparent. We have to be clear which is which: we should not kid ourselves that finding out which *var* genes are transcribed in a particular clinical syndrome, to take something which I would very much like to know, is going to have much impact over the next few years in the hospital in which we do the research.

Testing the fruits of research

Having generated good ideas, such as a promising ancillary treatment for cerebral malaria, a new regimen for quinine or whatever- the next requirement is to know quickly and definitively whether or not it works, and what it costs. We cannot afford to go on repeating studies which are just not quite big enough to be sure, nor powerful enough to convince policy makers. Of course, this is in no way a problem restricted to Africa, and the answer is in one sense simple: numbers, numbers, numbers. There has been a remarkable movement over the last fifteen years or so to ever bigger studies in clinical research in general but there are some particular problems that we face in Africa. For a start there are just not enough centres which can participate in such studies, given that they require a minimum in terms of infrastructure and personnel. The development of a research network for severe malaria through a MIM initiative is a very promising development, but we should not be complacent as problems remain. First, we have to recognise that whatever the altruistic motives of researchers, and I believe that in this area there *is* a very high level of humanitarian commitment, we cannot get away from the fact that there is a tension between the need for individuals and research groups to maximise their research outputs, and the desire to pool resources. In a nutshell, which would you rather have: a first author paper in the Lancet describing a ***promising*** reduction in coma resolution time in cerebral malaria, or be listed in the acknowledgements, with 48 others, in a ***definitive*** study of 2000 children which show that it was a fluke and that the intervention is useless? If we can solve this problem, and I think we can so long as funders really take it on board, there remains the concern that by their very nature the few sophisticated research units in Africa are really very untypical of the average under-resourced district hospital. What we really need is an approach that can mount large simple outcome trials in a network of such hospitals and this presents a formidable challenge.

Translation and sustainability

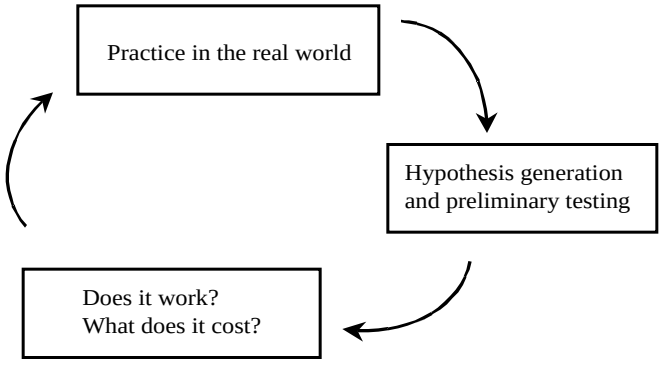
Finally having established that "wonderquin" at only 5 cents a dose can reduce case fatality by 20 %, we come to the real crunch issue: the translation of the research findings into practice. As researchers we tend to have a poor grasp on what is required. The first mistake we tend to make is the idea that there is ***a person*** in the ministry of health to whom it is only necessary to explain our most recent findings in order to change practice throughout the land. When this does not happen, as of course it never does, we complain that no one seems very interested in our findings. Of course the truth is that there is no such person. The whole process of policy formation and implementation is enormously more complex involving many individuals and groupings at different levels, within different departments and with many different priorities, all very pressing. Worse, many of the key parts of the chain are not in the ministry of health, but in other sectors such as finance, where decisions are taken on budgets for procurement etc.

Does this mean that all researchers have to engage in learning the arcane rules of the civil service and spend countless hours sitting outside the door of the permanent secretary? No, of course it would be a waste of time for us all to be doing this, but it is important that the research community and all other stake holders in health policy, find way of working together from an early stage if we are to avoid years of frustrating delay.

The second mistake we tend to make is to carry over our concept of ourselves as *malaria* researchers, researching on malaria. In the real world children do not turn up at health facilities neatly labelled as malaria, but as sick children in whom malaria may or may not be a major factor. It is important to realise that translation of research about malaria into useful

practice often involves a broadening of the approach, this is why the Integrated Management of Childhood Illness (IMCI) is such an important and central concept. The Division of Curative Services may sometimes be a more important target for ones networking than the national malaria control programme.

There are many reasons why perfectly good research does not end up being translated into practice, from failure to convey the information to the right people to problems at the other end of the line where hard pressed demoralised staff treat sick children. This brings us back to where we started, with the need for health systems research and operational research. The perspective which I have been trying to capture is shown in the Figure below, with a continuous interaction between what is happening, what could in theory be done, demonstrating that it works and is affordable and then translating it into practice and seeing its effect.



Room for Improvement?

So much then for the broader perspective - but all this does presuppose that there ***are*** things which clinical research can generate which will improve the outlook for children with severe malaria

Table 1 is taken from the soon to be published revision of the WHO guidelines on severe malaria. It is a list of interventions for severe malaria that have been suggested, but for which there is no evidence to support their efficacy. That does not mean that they are all useless - some may yet turn out to be important - but as yet, despite the fact that most have been talked about for many years, there is no evidence to support their use. One can look at this in different ways: a pessimist might say that there is not much chance of the next on the list doing much better, while an optimist would say we must find one that works soon!

Table 1: Cerebral Malaria: ancillary treatments not recommended

1.	Corticosteroids
2	Other anti-inflamatory agents
3	Other anti-cerebral oedema agents
4	Low molecular weight dextran
5	Adrenaline
6	Heparin
7	Prostacyclin
8	Oxypentifylline
9	Hyperbaric oxygen
10	Cyclosporin A
11	Hyperimmune serum
12	Iron chelators
13	Dichloroacetate
14	Anti-TNF antibodies

One thing that one notices from the list is that many of these drugs would not be found close to hand in an average hospital. Now this of course may not matter, but it does raise the issue of whether we are happy that the things we do have available are being used in an optimum way? One might hope that this is the case because, after all, there are only very few

interventions available to us which can truly be described as potentially life saving and it ought to be possible to use them properly. These are listed in Table 2, and in fact with the addition of oxygen this would pretty much be the key list of things that could make a critical difference to any very sick child in a district hospital, whatever the diagnosis.

Table 2 Treatments available in most hospitals and potentially of major importance in severe malaria

1. Antimalarials
2. Antibiotics
3. Sugar
4. Fluids
5. Blood
6. Anticonvulsants
7. Antipyretics
8. Common sense

What I want to do now is run briefly through a few examples from this list and try to convince you that, far from all being sorted out, there are a large number of key research issues that need tackling. One of the things that did strike me in being involved with the preparation of the breakout sessions on severe disease for this congress, was the dearth of submissions on central and very difficult issues of practical management. In saying this, it is important to stress that I am not presenting a sort of Luddite argument that we should limit our research strategies to such a list. At Kilifi we have our fluorescent-activated cell-sorter and PCR humming along as enthusiastically as in any other research centre. Nonetheless, I do think there is a risk of going for some areas of research because, basically, they are easy. It is easier for instance, to measure the levels of the latest cytokine in a nice clean laboratory, than to concentrate on the messy and difficult business of looking after sick children in hot overcrowded and under-resourced hospital wards.

Anti-malarials

One might think there is not a lot to say here. Quinine is the standard treatment, it is widely available, we have a lot of experience and resistance is not yet a problem with it: But resistance will come, quinine is not an innocuous drug and it is far from clear that we do have treatment regimes absolutely right.

The previous talk stressed the speed with which children die of malaria and yet quinine is rather a slowly acting drug. This is one of the things which make the qinghasou /artemesinin group potentially very attractive as alternatives to quinine. Those who attended the breakout on Monday will have heard Nick White present the meta-analysis of the artemether-quinine trials. The basic message is that artemether is about as good as quinine. Some people have been rather disappointed at this, hoping that it would be dramatically better, but I would argue that it is pretty good news to have a new group of potentially affordable drugs that are as good as one of the most important drugs we have. I think there is also a strong argument that we may have somewhat loaded the dice against artemether by doing trials in patients with cerebral malaria. On the face of it, it makes sense to test your most exciting drugs in your most dramatic cases, but there is a strong argument that we should now be looking at the use of these drugs earlier in the story. The other new slant is that many people now feel that there are strong reasons for thinking that artesunate may have quite major advantages over artemether, and if such trials are to be carried out it will be necessary to develop the sort of multicentre facility discussed above.

Antibiotics

Next on out list is antibiotics and one might wonder why are we talking about antibiotics to treat malaria. Our recent experience in Kilifi is that a significant proportion of children with severe malaria also have concurrent bacteraemias and that this syndrome is associated with very high mortality. This a potentially very important management issue. It also presents interesting ethical issues: should we do randomised trials if observational studies reveal something for which we already know we have a treatment in broad spectrum antibiotics?

Our feeling at Kilifi is that our local data is so convincing, at least to us, that we now treat all children under three years who have severe malaria with broad spectrum antibiotics. Clearly this whole story needs to be sorted out: is the same true elsewhere, and what is the optimum management?

Sugar

One of the cheapest and most widely available life-saving interventions for malaria is sugar. Hypoglycaemia is strongly associated with death. It is also a major risk factor for neurological sequelae and for cognitive deficit, even in children with no obvious sequelae.

In most series of children with severe malaria, around 15% have hypoglycaemia on admission. However, something less well appreciated is that other children who are normoglycaemic on admission often develop hypoglycaemia despite routine 5% dextrose as part of management fluids. More worrying in our experience is that children already known to have been hypoglycaemic and who have received 50% dextrose and then maintenance with 10% dextrose still commonly develop recurrent hypoglycaemia. This data is from a setting where we can afford to monitor glucose regularly and at any deterioration. Most hospitals are not able to provide regular and quick measurements. Glucose sticks are the obvious answer, but they are prohibitively expensive. Thus it seems certain that one of the most important complications of severe malaria is often not recognised or managed.

There is no simple answer to this problem. Some have suggested using sugar solutions through nasogastric tubes as a potential approach. This initially has the feel of being good practical sense, but the problem of recurrent hypoglycaemia, while receiving intravenous dextrose, suggests that it is unlikely that one could keep up with demand by this route. Testing nasogastric regimes presents some interesting ethical problems: hypoglycaemia is considered by most people to be an emergency, given its potential for brain damage. Any research centre that can measure levels quickly enough in a kinetic monitoring of nasogastric glucose will certainly be well set up to give definitive intravenous treatment. Can it be justified to delay this? But if not then how can one ever be sure of the safety or efficacy for recommendations to be used in less optimum conditions? Hypoglycaemia is one of the most important problems we face and so far as I can see there are no easy answers. It does, however, seem that there is something wrong with our perspective when this congress did not receive a single abstract on this issue- a major cause of death and sequelae for which the treatment is cheap and widely available.

Blood

In the previous talk it was clear that the overlap of anaemia and respiratory distress is a common situation associated with a very high mortality, for which relatively cheap and widely available treatment – blood - is available. So what is the issue here? If one looks at protocols, where they exist, or talks to clinicians across Africa, there remains almost unanimity on the idea that transfusions in these pale breathless children should be given very slowly, minimising volume by the use of packed cells and further by the use of diuretics. The reasoning, hallowed by generations of repetition, is that these children are in congestive cardiac failure.

However, we now know that the usual reason for these children being breathless is that they are severely acidotic. There is not time to explore here the pathophysiology of what is going on to make these children so severely acidotic, but I will summarise a lot of work by colleagues by saying that two major factors are anaemia and hypovolaemaia. Now, hypovolaemic acidosis is not unique to malaria: it is a common end stage presentation of many life-threatening conditions all over the world. The management of such children turning up at casualty or on intensive care units in Europe, America or here in Durban involves an absolutely key component: *rapid* resuscitation, often with large volumes of fluid. You will note that this is the exact opposite of what I have said is the practice in malaria, because the cause has been presumed to be different.

So we have a situation where we have diametrically opposite possibilities for the delivery of a life-saving intervention. If those who worry about congestive cardiac failure are right, then rapid resuscitation with blood will put the child at high risk of dying through volume

overload. If the scenario for the development of severe acidosis is right, then the traditional approach will fail to provide a life-saving treatment to the highest risk group. This would seem to be a pretty important research question, but again the congress received not a single abstract on the management of acute severe malarial anaemia. However, this seemed so important that we have arranged within this afternoon's session to have two presentations on this area.

Concluding Remarks

I want now to draw together and summarise what I have been saying. Firstly, I stressed that the really key issue is to prevent events getting as far as severe malaria. Despite this, we expect severe malaria to remain a massive clinical problem in African hospitals for many years to come. Therefore we need a strategic approach involving short, medium and long term strategies to reducing case fatality. I have concentrated on what could be called short-term research because I have argued there is great urgency for this. I have also argued that we have not been active enough in making what is actually happening now, in real hospitals across Africa, the centre point from which we set our research objectives. I have argued that there is a need for a much greater capacity to take promising interventions through to a definitive answer in short time, and subsequently that much greater attention to the process of translation of research findings into policy is required.

On the subject of what specific research can be expected to make a difference, I have steered clear of some approaches that might be considered more sophisticated or exciting (although I don't agree with this perception), and instead have concentrated on the really quite limited set of key options that may be life-saving in district hospitals. I have argued that in many, indeed I would say all, cases there are major unresolved research issues which, if not actually ignored, have certainly not received the attention they deserve. I hope that I have conveyed a sense that far from there being little that can be done, there is in fact an enormously important challenge for all of us here, whether we are researchers, policy makers or implementers. It has been a privilege to have the opportunity to share these thoughts and I feel very hopeful that the unique opportunities provided by MIM and a congress such as this will allow us to rise to this challenge.

BREAKOUT SESSIONS: MANAGEMENT OF SEVERE MALARIA

Programme

1. Management of Severe Malaria and Antimalarial Drugs : Joint Session
Chair: Dr. Pascal Ringwald and Dr. Piero Olliaro
Rapporteur: Dr. Didier Diallo, Dr. Dora Akinboye, Dr. Eric Achidi

Presentations (20 mins)
1. Implications of drug resistance and loading dose in treatment of severe malaria in Africa - Akintunde Sowunmi.
2. Current practices and Potential Role of antimalarial suppositories in management of severe Malaria in Rural Areas - Melba Gomes.
3. Meta-Analysis of arthemether and quinine trials in management of severe malaria - Nick White.

Abstracts (5 min each)
1. La quinine en solution intrarectale est efficace dans le neuropaludisme et les acces graves de l'enfant en Afrique - Hubert Barennes.
2. Artesunate suppositories in the treatment of moderately severe malaria in Malawian children - Madalitso Tembo.
3. A randomised, placebo controlled, double-blind study of the tolerability and efficacy of Artesunate plus sulphadoxine/pyrimethamine combinations vs. Single-agent sulphadoxine/pyrimethamine for the treatment of uncomplicated falciparum malaria - Lorenz von Seidlein.
4. Comparative efficacy of chloroquine and co-trimoxazole in acute uncomplicated falciparum malaria in children - Adegoke Falade.

2. Management of Severe Malaria II
Chairs: Professor Ogobara Doumbo, Dr Charles Newton
Rapporteurs: Dr Hubert Barennes, Dr. Mike English

1. Severe Malaria in African Children (SMAC) network - Terrie Taylor.
2. Evidence of moderate and severe brain swelling in paediatric cerebral malaria: an autopsy study - R.A. Carr.
3. Retinal findings as a prognostic indicator in cerebral malaria - Jeff Ajewole.
4. Phenobarbitone prophylaxis in childhood cerebral malaria - Jane Crawley.
5. Malaria – are developmental problems associated with severe disease? - Penny Holding.
6. Effect of Paracetamol on parasite clearance in Kenyan children with severe malaria - Faith Osier.
7. Bacteraemia complicating severe malaria in children - James Berkley.
   Discussion

3. Management of Severe Malaria III
Chairs: Dr Ayo Palmer and Professor P Kremsner
Rapporteurs: Dr Hubert Barennes and Dr. Mike English

1. The spectrum of severe malaria in The Gambia and its relationship to mortality - Stanley Usen.
2. Susceptibility of red blood cells from children with severe *Plasmodium falciparum* anaemia and age matched controls of erythrophagocytosis - John Waitumbi.
3. Binding of complement of C3d to erythrocytes is associated with anaemia in acute childhood malaria - Bamenla Goka.
4. Red cell deformability in severe malaria - Kevin Marsh.
5. Metabolic acidosis: the role of intravenous fluids and blood - Mike English.
6. Metabolic acidosis: the role of dichloroacetate - Sanjeev Krishna.

7. Discussion.

Summary Report: Management of Severe Malaria

The problem of severe malaria was explored in two plenary talks and two and a half breakout sessions. Two broad themes were addressed during the plenaries:

- a summary of the current state of the art in clinical research on severe malaria
- an examination of the role of clinical research in the broader objective of malaria control.

The breakout sessions provided the opportunity for short presentations on a wide range of specific clinical issues and wherever possible, it was attempted to set discussion in the framework of the wider perspective taken in the plenaries.

The main issues and themes to arise are summarised in brief below. A few useful overarching points are highlighted :

· Severe malaria indicates failure of control- an absolute priority is the early and appropriate treatment of febrile illness to prevent further deterioration. In this context, work on identifying affordable safe drugs, preventing the development of resistance by using combinations, and delivery to the point where most treatment takes place (the home) all require maximum support.

· Nonetheless, even with the most optimistic predictions of success, severe malaria will continue to form one of the single biggest problems at health centres and hospitals in Africa for the next twenty years.

· Therefore, a research strategy is required which includes short, medium and long-term objectives. The long-term objectives of better understanding the pathophysiology in order to develop new therapeutic approaches remains important, but it should be recognised that there is a dearth of information on how best to use even the few interventions that we have and that are known to be potentially life saving. This must be addressed with urgency.

· In order to do this it is important to know what is actually happening on the ground where the majority of cases are treated. This will define the agenda, at least for short and medium term research strategies.

· These should concentrate on taking promising approaches as quickly as possible from pilot stage to definitive study. Such studies will need to be large enough to produce convincing answers and avoid the need for repeated small trials. This will necessitate the formation of the capacity for carrying out multicenre studies both within and between countries

· Early and close collaboration with the appropriate divisions of Ministries of Health is essential if clinical research is to be translated into practice. In many cases, current levels of collaboration are too little too late and do not result in a sense of ownership for those individuals and groupings who will be charged with implementation. Although collaboration with control programmes is essential, it should also be recognised that the required emphasis on the sick child means that collaboration with other groupings, particularly those covering curative services, will be equally important.

Summary of main issues discussed

The following areas were some of those identified as either areas of relative ignorance or those requiring further development. Exploiting these areas will require active input from African scientists, the development of working links between them, and an increased level of communication at an early stage with policy makers. Policy makers themselves may do much to encourage the development of indigenous research by recognising its value, facilitating its execution and highlighting areas requiring attention.

- ***Description of disease:*** The heterogeneity of severe disease means that each country will require more detailed knowledge of its own current pattern and burden of disease since this may vary between different areas / countries. Ideally, this information should come from health facility based sources and the community. Such data will be invaluable for planning effective, appropriate control strategies (including resource allocation).

- ***Definitions of disease:*** Consensus definitions of disease syndromes may facilitate information sharing and understanding, and make the use of research information easier for policy makers.

- ***Malaria in the context of the sick child:*** Managing clinical malaria must be considered part of an overall approach to delivering effective treatment to sick children since malaria often overlaps with other diseases.

- ***Early treatment of mild / moderate disease:*** While the natural history of severe disease remains poorly understood, there is clearly a need to examine the possibility that early effective treatment at community / peripheral levels may reduce the burden of severe disease. New drugs (e.g. Artemsinin derivatives) and routes of administration (e.g. rectal) make this particularly pertinent.

- ***Pathogenesis of Disease:*** Many areas still remain poorly understood, perhaps most obviously (but not exclusively):
  The mechanisms resulting in coma
  The natural history of anaemia
  Why severe anaemia may take such dramatically different clinical forms
  Acidosis
  Hypoglycaemia
  Seizures / convulsions
  The development of neurological sequelae

- ***The long-term effects of severe malaria:*** In particular neuro-psychological sequelae and post discharge mortality and morbidity.

- ***The Ethical issues involved in research on severely ill children in Africa:*** Cultural heterogeneity may demand the development of locally appropriate approaches to these issues. In particular, the role of community consent and the need for individual consent / assent.

- ***The training of African clinical researchers:*** Including training in research at undergraduate and post-graduate levels as well as training in how to communicate research findings to the control community.

- ***Systems research to identify current strengths and weaknesses in management:***
  For example, the ability to deliver such interventions as safe blood for transfusion.

Improved understanding in all of the above areas might facilitate ***evidence based practice*** in malaria management and control. However, a key difficulty is the current in-ability of clinical researchers in Africa to test new and current approaches on the scale required to answer questions of true effectiveness. This is particularly important when the costs of different treatment strategies are being considered. Tackling this deficiency is a major but vitally important undertaking requiring multiple partners. The first steps of this process are being taken with:

The Severe Malaria in African Children (SMAC) Network
This network aims to develop:

- A working network of clinical researchers across Africa who might take part in large, simple intervention trials primarily with mortality as the outcome.

- The methodology required to undertake such trials.
- The infrastructure required to undertake such trials.

While the long-term nature of such a venture in Africa, a continent with major communication difficulties, poses particular problems, the need for such a structure is great. Basic research suggesting the usefulness of an intervention demands that its effectiveness be examined. In many cases this can only be achieved using a multi-centre approach, a lesson already learned in developed economy health-care systems. A particular challenge in Africa may be to develop the ability to test interventions at the level at which they must eventually often be used, the small hospital or health centre. This may require the development and testing of strategies that are simpler than those to be used in research centres. Examples of such interventions might include:

- The use of novel antimalarial drugs / formulations (including combination therapy)
- Protocols for intravenous fluid use and / or blood transfusion
- The treatment of hypoglycaemia

Afterword

A central theme to emerge in all of the above is the need to focus short and medium term clinical research on what is happening on the ground and on interventions that could make a real difference now. This will require high quality clinical research and trial design, but it will also require considerably more investment in health systems and operational research. One of the issues that funders will need to take on board is the inevitable tendency of the current scientific ethos to favour high profile publication. Thus, small studies of cutting edge therapies carried out by identified individuals win out over large studies of more mundane (but potentially more useful) approaches carried out by large collaborative groups (who do not receive much credit when their next grant renewal is due). It is difficult to see how clinical research in Africa can be given impetus along the lines described above, unless this fundamental issue is addressed.

MALARIA IN PREGNANCY

Plenary Presentation

Malaria Control for Pregnant Women.
Umberto D'Alessandro

Summary Report on Breakout Session

Programme

Summary Report

PLENARY PRESENTATION

Malaria Control for Pregnant Women

Umberto D'Alessandro, Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium.

The prevalence of malaria is increased during pregnancy compared to the non-pregnant state (Gilles et al, 1969; Brabin et al, 1988; Kortman, 1972; Brabin et al, 1990a). Susceptibility to infection and the severity of clinical manifestations are determined by the level of pre-pregnancy immunity which, in turn, depends largely on the intensity and stability of malaria transmission (Mutabingwa, 1994). In highly endemic areas, such as most of sub-Saharan Africa, the effects of malaria on mother and foetus are less severe than in areas with low or unstable transmission, but malaria still has important consequences for pregnancy, especially in primigravidae. It has been repeatedly reported that primigravidae usually have a higher prevalence of malaria infection (peripheral or placental) as compared to multigravidae (Keuter et al, 1990; Mvondo et al, 1992; Bulmer et al, 1993; Meuris et al, 1993; Mutabwinga et al, 1993), and that the difference between infected and non-infected women in mean Hb levels (Kortman, 1972; McGregor, 1984; Brabin et al, 1990) as well as in mean birth weight (Jelliffe, 1968; Kortman, 1972; McGregor et al, 1983) are more marked in primigravidae than in multigravidae. However, multigravidae are also vulnerable to malaria as it has been shown by recent data from Senegal. The incidence of malaria attacks during pregnancy as compared to control time periods (before or after pregnancy) in the same women was significantly and substantially increased also for multigravidae up to their fifth pregnancy (Diagne et al, 1997). This makes the proposition of limiting malaria chemoprophylaxis to primigravidae not only impractical from an operational point of view but also difficult to justify in view of the above data. There are still a few questions to be answered in terms of the consequences of malaria for pregnant women and their offsprings. For example, the role of malaria as a contributing factor to abortion, perinatal mortality and prematurity is unknown (Menendez, 1995), although for the latter a significant reduction after the implementation of a national programme on insecticide-treated nets (ITN) has been reported (D'Alessandro et al, 1996). The effect of malaria during pregnancy on the infant's susceptibility to infection and on mortality is also unknown, although it is likely that increasing the mean birth weight as result of malaria prevention would increase the chances of survival.

Since 1964, about 300 papers reporting, directly or indirectly, on malaria control measures during pregnancy have been published. However, this is still a controversial subject. A recent Cochrane review on malaria prevention in pregnant women identified only 14 trials meeting the authors' strict inclusion criteria (Gulmezoglu & Garner, 1999). The trials used different antimalarial drugs (chloroquine, pyrimethamine, mefloquine dapsone-pyrimethamine) and different chemoprophylaxis regimens (daily, weekly, fortnightly and monthly). A significant decrease of antenatal parasitaemia was found in most of the studies (Fleming et al, 1986; Greenwood et al, 1989; Mutabingwa et al, 1993a; Nosten et al, 1994; Nyirjesy et al, 1993). A small effect on packed cell volume was detected, although it appeared to be confined mainly to primigravidae (Hamilton et al, 1972; Greenwood et al, 1989; Nosten et al, 1994). There was a trend towards a higher mean birth weight, mainly in primigravidae (Morley et al, 1964; Hamilton et al, 1972; Greenwood et al, 1989; Cot et al, 1992; Nosten et al, 1994; Nyirjesy et al, 1993). None of the trials, because of their relatively small size, had sufficient power to detect a possible effect on perinatal and neonatal mortality and surrogate and intermediate outcomes of infant death, which include placental parasitaemia,

are of doubtful significance (Gulmezoglu & Garner, 1999). The conclusions of the Cochrane review is that given the existing evidence, effectiveness of prophylaxis on relevant outcomes is not strong: it seems to protect from illness in the mother and increase birth weight in primigravidae. Study sizes mitigate against any conclusions in terms of obstetric morbidity or fetal/infant mortality (Gulmezoglu & Garner, 1999). However, several trials were not included in the above review because they did not meet the necessary requirements or have been published after the review. It is worthwhile considering that the results of the largest chemoprophilaxis trial ever done during pregnancy was excluded because of suspected bias in the allocation of the 4 regimens under evaluation. The study, the Mangochi Malaria Research Project carried out in Malawi, evaluated three different chloroquine (CQ) regimens against mefloquine (MQ) (Steketee et al, 1996). In each of the 4 centres participating to the trial where pregnant women were enrolled, one of the three CQ regimens was compared to a MQ regimen by alternation (days of the week). The method reported should have led to a 1:1 ratio of women given mefloquine:chloroquine. However, there were four times as many women in the chloroquine group (3077 vs 1032) and this is the reason why the results were not considered for the Cochrane review (Gulmezoglu & Garner, 1999). Nevertheless, the results can still be of relevance when considering the impact of chemprophylaxis during pregnancy. At the time of the study chloroquine resistance in Malawi was already high. The risk of persistent or breakthrough malaria infection was much higher among women on CQ as compared to those on MQ (OR: 30.9 and OR: 11.1 respectively) (Steketee et al, 1996). The risk of peripheral or placental parasitaemia was also higher in women on CQ (OR: 8.7 and 7.4 respectively). The percentage of low birth weight babies was lower in the MQ than in the CQ group (12.5% vs 15.5%). These results indicate that an effective antimalarial drug can prevent malaria infection during pregnancy and can have a beneficial effect on its outcome.

An alternative approach is the administration of intermittent presumptive treatment, which may achieve equal efficacy to continuous chemoprophylaxis. This has been investigated in Malawi where a two-dose regimen of sulfadoxine-pyrimethamine (SP) (one dose in the second trimester followed by a second dose at the beginning of the third) were compared with one dose of SP or one treatment of CQ followed by weekly CQ. The results show a significant impact of the 2-dose SP regimen on peripheral and placental parasitaemia and a tendency towards a higher mean birth weight and a lower percentage of low birth weight babies (Schultz et al, 1994). A recent published trial carried out in Malawi found a significant difference in mean birth weight and percentage of LBW in women who had received two or three doses of SP during pregnancy compared to those who had received only one dose (Verhoeff et al, 1998). However, 1. the study was not a randomised controlled trial and assigned different doses of SP according to the weeks of gestation at time of first antenatal clinic; 2. data were available only for 31% of the women recruited; 3. the number of SP doses did not have any effect on placenta or peripheral parasitaemia at delivery and on Hb concentration. Two additional trials carried out in Kenya compared intermittent treatment with SP with placebo or routine case management. One showed a significant decrease of severe anaemia in pregnant women on SP but not on the occurrence of LBW or on mean birth weight (Shulman et al, 1999). The other showed also an impact on mean birth weight and the percentage of LBW babies (Parise et al, 1998).

SP intermittent treatment seems effective in preventing some of the consequences of malaria infection in pregnant women. However, some questions still remain. Before the 16th week of pregnancy SP is not recommended because of concerns on possible

teratogenicity (Phillips-Howard & Wood, 1996). Furthermore, SP intermittent treatment has been compared either with a placebo or with weekly CQ prophylaxis, which was likely to be ineffective because of the high level of resistance already present. None of the above studies compared effective weekly malaria chemoprophylaxis with effective intermittent treatment. This should caution us in implementing SP intermittent treatment everywhere, even in places where CQ remains still the first line treatment. There have been several reports on the interaction between HIV infection and malaria during pregnancy (Verhoef et al, 1999). Two doses of SP during pregnancy seem insufficient to confer adequate protection to HIV+ women and the number of doses to be given to this particular group of women is still unknown. The lower efficacy of SP when given together with folic acid raises the question on whether these 2 drugs should be given together to pregnant women.

Insecticide-treated nets (ITN), which are effective at reducing malaria in children and adults (D'Alessandro et al, 1995), offer a possible alternative approach to the control of malaria in pregnancy. However, the evidence on whether ITN or just untreated nets during pregnancy are of practical benefit is insufficient (Gulmezoglu & Garner, 1999). The first trial was carried out in 3 refugee camps on the Thai-Burmese border (Dolan et al, 1993). A significant reduction in the incidence of *vivax* and *falciparum* malaria was observed in only one camp but a significant reduction of anaemia was recorded in all 3 camps. The size of the net significantly influenced the degree of protective efficacy; malaria and anaemia occurred more frequently in the group using untreated single-size bednets distributed by the investigators than in those using 'family untreated bednets' which were large enough for 2 or 3 persons. No beneficial effect of ITN on birth weight was shown. Another trial carried out in Kenya and involving about 500 primigravidae was unable to show any significant impact of ITN on different factors (severe anaemia, peripheral and placental parasitaemia, birth weight)(Shulman et al, 1998). However, the ITN national programme in The Gambia had some impact limited to the malaria transmission season on primigravidae (D'Alessandro, 1996). Mean birth weight, prevalence of parasitaemia at 32 weeks of gestation, percentage of premature babies were significantly different in primigravidae living in villages where nets had been treated with insecticide.

Whatever the strategy used to control malaria during pregnancy and although this should cover all pregnant women, primigravidae remain the most vulnerable group to be specifically targeted. Unfortunately, this is the group that is more difficult to reach. In The Gambia, for example, the mean age of 651 primigravidae was 17 years, most of them were farmers and illiterate. Although most of them attended an antenatal clinic at least once (mean number of attendance: 4), received some iron and folic acid supplementation, only a small minority received some chemoprophylaxis (D'Alessandro, 1996). The iron and folic acid supplementation did not have any effect on mean PCV levels, the percentage of anaemia (Hb≤8) at 32 weeks of gestation was 18%.

Despite available data on different interventions retain some uncertainties, it is possible to reduce the burden of malaria among pregnant women, just by using current knowledge. However, one of the major problems for programme managers and implementers remains how to translate the available information in feasible and sustainable programmes. How to improve the delivery and coverage of such interventions, particularly for primigravidae? There is the need of promoting collaboration between scientists and policy makers/health managers in order to answer these questions and so doing, contributing to the decrease of the burden of disease among pregnant women. A recently developed initiative, **PRE**gnancy

Malaria and **A**naemia (PREMA), aiming at answering the above needs will try to facilitate the communication between control and research communities. This is an essential step for optimizing the implementation of excisting research findings.

The proposed activities of PREMA are:

1. To create a compendium of current national malaria control policies targeted at pregnant women in African countries in order to know what is done and how this differs between countries;
2. To review available data on the efficacy, effectiveness, acceptability and operational feasibility of different strategies for malaria control during pregnancy and to produce guidelines for national programmes;
3. To identify gaps in knowledge and to develop appropriate research protocols when needed;
4. To create consensus documents and position papers on issues relating to malaria in pregnancy for wide dissemination through peer reviewed journals and to Governments, NGOs and donor agencies;
5. To sensitise and inform, by means of a newsletter and other publications, policy makers and national governments of research findings on malaria in pregnancy and of their implications for malaria control programmes in endemic areas;

Strategies aiming at improving the health of pregnant women in malaria endemic countries will be successful only if a dialogue between scientists and implementers is promoted and the current scientific knowledge applied in the best possible way.

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BREAKOUT SESSION: MALARIA IN PREGNANCY

Programme

Malaria in Pregnancy

Chairs: Dr. Theonest Mutabingwa and Dr. Steve Allen

Rapporteurs: Dr. Clara Menendez, Dr Umberto d'Alessandro

1. Basic science question, where are we now? - Clara Menendez (10 mins).
2. Pregnancy associated enhanced susceptibility to malaria persists three months after delivery - Nefissatou Diagne (5 mins).
3. *Plasmodium falciparum* and pregnancy in Cameroon: malaria prevalence of T cells responses - R. Magnekou (5 mins).
4. Data needs for preparing strategies for malaria control in pregnancy – Caroline Shulman (10 mins).
5. Assessment of malaria in pregnancy and antimalarial drug resistance, Koro, northern Mali – Mary Mungai (5 mins).
6. Prophylaxis in pregnancy - Pascal Magnussen (10 mins).
7. Managing malaria in pregnancy - Alan Macheso (10 mins).
8. A randomised controlled trial on malaria control in pregnancy in Ejisu-Juoben District, Ghana - Edmund Browne (5 mins).
9. New tools for measuring the impact of malaria control in pregnancy - Steve Allen (10 mins).
10. The role of bednets for malaria control in pregnancy. - Jo Lines (5 mins).
11. Malaria and HIV. - Bernard Nahlen (10 mins).
12. Recommendations from a recent WHO Expert meeting. A. Rietveld, Alastair Robb (5 mins).

General discussion.

Setting a Research Agenda relevant to control programmes. - Clara Menendez (Rapporteur).

Establishing the Pregnancy and Malaria Anaemia (PREMA) Network. - Umberto d'Alessandro (Rapporteur).

Summary Report: Malaria in Pregnancy

Clara Menedez reviewed what it is known in terms of biology and control of malaria during pregnancy. Several gaps in knowledge as well as controversies were identified. The mechanisms involved in the increased risk of malaria are still not completely understood. The effect of maternal parity and the impact of protection against malaria during pregnancy on the infants risk to malaria are unknown. The efficacy of intermittent antimalarial treatment at different immunity levels and the efficacy of impregnated bed nets compared with that of regular chemoprophylaxis or intermittent treatment needs also to be investigated. The interaction of sulfadoxine-pyrimethamine intermittent treatment with folic acid on the risk of malaria needs to be clarified as well as the potential use and efficacy in pregnancy of future malaria vaccines. Whether protection in high endemic areas should be restricted to specific groups of pregnant women at risk (primigravidae, severely anaemic, HIV seropositive) needs to be discussed.

N. Diagne presented data from Senegal showing that women of all parities had a higher incidence of clinical malaria during their pregnancy and early postpartum supporting the hypothesis that pregnancy-associated immuno-suppression, but not parasite sequestration in the placenta, is the leading mechanism involved in maternal malaria.

Rosette Magnekou confirmed that primigravidae are more susceptible than multigravidae to malaria infection and that the II trimester is the most vulnerable period when a down-regulation of T cell proliferative responses has been shown. Only 4 out of 24 countries included malaria in pregnancy as part of their plan of action (C. Shulman). A recent trial in Kenya showed a considerable impact of SP intermittent treatment on anaemia in primigravidae. The Kenya Malaria Control Unit was already in the process of changing policy to intermittent SP for women of all parities, based on evidence from Malawi, Kisumu and Kilifi. According to Shulman, although there are a number of questions requiring clarification, it is important not to wait until we have all of the answers before research findings are translated into policy. The new strategy should be implemented and at the same times safety and effectiveness should be monitored. The results of randomized, double-blind, placebo controlled intervention trial on chloroquine prophylaxis and iron/folic acid supplementation in Hoima District, Western Uganda were reported by Pascal Magnussen. Chloroquine prophylaxis and iron/folic acid supplementation both increased maternal Hb compared to case management and the effect increased with duration of prophylaxis. There was no difference in the increase in Hb between the two groups. Both chloroquine and iron/folic acid had additional advantages over case management alone on maternal Hb and fetal outcome. Alan Macheso reported on the Malawian experience of introducing SP intermittent treatment for pregnant women. In 1997 data from 2 sentinel sites indicate that maternal (5%), placental (6%) and cord (2%) parasitaemia are very low among pregnant women. However, there are problems with HIV + women.

A discussion after this first round of presentation followed. What is the impact (positive/negative) of chemoprophylaxis during pregnancy on infant mortality? Considering the present knowledge it is impossible to use a placebo to investigate such a question. It was proposed to use birth weight to predict the impact on infant mortality as it is known that this is linked to child survival. The evidence of the impact of SP intermittent treatment on birth weight is weak. Why this strategy should be promoted as policy? It was

pointed out that it was ethically impossible to look at anaemia and BW at the same time as anaemic women should be treated. However, the effect on maternal anaemia was large, at least in Kenya and this could justify the implementation of such policy. Anaemia in pregnant women is multifactorial and all of them should receive a supplement of iron and folic acid.

Edmund Browne presented the design of a trial comparing monthly chloroquine treatment with monthly SP treatment and with routine antenatal care in primigravidae and secundigravidae. The study is currently carried out in Ghana and aims at recruiting a total of 660 pregnant women. A new way of monitoring malaria transmission or malaria control measures in pregnancy was presented by Steve Allen. The normogram is based on the percentage low birthweight in primigravidae (Y axis) and the odds ratio for low birthweight in primigravidae compared to multigravidae (X axis). The normogram distinguished longitudinal changes in malaria exposure related to season and changes in antimalarial drug policy. As birth weight and parity are routinely recorded in many delivery centres across Africa, the normogram provides a simple, available and inexpensive tool for monitoring malaria transmission and exposure in pregnant women. Jo Lines discussed the role of insecticide-treated bednets (ITNs) on malaria control in pregnancy. It is still unclear whether ITNs give an additional benefit to pregnant women in terms of malaria control. They reduce exposure but is this enough to prevent the consequences of malaria infection? The interaction between malaria and HIV infection were discussed by Bernard Nahlen. HIV infection results in malaria-like symptoms and consequently in over use of antimalarial drugs. Aafje Rietveld presented the recommendations concerning malaria control in pregnancy from a recent WHO expert meeting.

The role of ITNs in malaria control during pregnancy is not clear. The question asked is whether the studies carried out so far had the power to detect such an effect. However, it is obvious that ITNs, even if they have an impact, it is not as big as that on mortality in children. Iron supplementation should be given to all pregnant women as there is no doubt that this is beneficial. The discussion pointed out also that future studies on pregnant women must avoid the use of placebo as the administration of chemoprophylaxis or intermittent treatment with SP has shown a clear benefit. Therefore, it would be unethical to have a control group only on placebo. The normogram on birth weight could be used to monitor the impact of the introduction of SP intermittent treatment.

Background

- malaria in pregnancy is a major cause of maternal mortality, maternal anaemia and low birthweight (LBW) in endemic areas
- the problem is often unrecognised because infected women are usually asymptomatic
- case management alone is not effective in preventing the adverse effects of malaria during pregnancy
- Preventive measures have clearly showed a positive impact on pregnant women and newborns

Research Priorities

Short-term

- appropriate tools are needed to monitor the effectiveness of current control programmes
- new methods are needed to improve the implementation and compliance with control strategies (eg. by the involvement of TBAs)
- monitoring the effectiveness of impregnated bednets in different endemic settings
- the cost-effectiveness of interventions in different settings needs to be assessed

Medium-term

- assessment of the combination of different preventive measures (eg. chemoprophylaxis/intermittent treatment and impregnated bednets)
- comparison of intermittent treatment (sulphadoxine-pyrimethamine) with regular, efficacious chemoprophylaxis
- more information regarding the efficacy of intermittent treatment with sulphadoxine-pyrimethamine in different endemic settings
- the negative interaction between HIV and malaria infection during pregnancy, in particular an increase in the vertical transmission of HIV and the increased susceptibility to malaria in HIV+ women
- the potential health implications of an increase risk to malaria in the post-partum period need to be explored
- the interaction between antifolate antimalarials and folic acid supplementation has to be assessed

Long-term

- new agents need to be developed to cope with the emergence of resistance to current drugs
- the importance of protection early in pregnancy needs further assessment
- more investigation of the mechanisms involved in the increased risk to malaria in pregnancy (eg. the role of binding to chondroitin sulphate)

Implications of current research results for the treatment and control of malaria

- case management alone is not effective in preventing the adverse effects of malaria during pregnancy
- there is clear evidence that protection should be offered at least to all primigravidae, women with severe anaemia including sickle cell disease and HIV+ women. In practice it may be more cost-effective to offer protection to all pregnant women. Questions remain regarding the choice of the drug, dosage, mode of delivery and implementation
- current strategies may be less effective in HIV+ women and this should be taken into account when planning and selecting interventions
- selection of the currently available preventive tools such as chemoprophylaxis, intermittent treatment and insecticide-impregnated bednets will need to be determined by local conditions
- it is likely that other interventions will need to be used in addition to impregnated bednets
- all women in endemic areas should receive haematinics during pregnancy
- interventions aimed at preventing malaria infection and its consequences during pregnancy need continuous monitoring. Key outcome measures are LBW

and maternal anaemia. The normogram for the excess-risk of LBW in primigravidae is a promising tool for the former.

Mechanisms for strengthening links between control and research communities

A recently developed initiative, PREgnancy Malaria and Anaemia (PREMA), is an attempt to facilitate communication between control and research communities. It is recognised that this is an essential step for optimising the implementation of existing research findings.

Research capacity needs

The effective development and implementation of control programmes will need inputs from several disciplines, including among others social anthropology, health economy. Training will also be needed to improve the ability of programme managers to monitor the impact of different intervention. There is also an urgent need for African scientists to be trained to undertake basic research.

ECONOMICS OF MALARIA

Plenary Presentation

Is Malaria Control Cost-Effective?

Anne Mills

Breakout Sessions

Programme

1. Demand for Malaria Treatment and Prevention.
2. Supply Issues and Markets
3. Public Policy

Summary Report

PLENARY PRESENTATION

Is Malaria Control Cost-Effective?

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Introduction

As an economist, I am most grateful for the invitation to speak at the start of this important meeting, and particularly glad of the recognition that economics has much to offer both researchers and control programmes who seek to tackle the burden of malaria. A number of you may be concerned that I am going to present puzzling demand and supply curves, show strange equations, or talk about choosing between apples and pears (for those of you not familiar with elementary economics, issues of choice are often introduced in this way). I am going to do none of that, but rather to present the key messages from recent work on the economic burden of malaria and the cost-effectiveness of malaria control. I will end by highlighting key research needs identified by the economic analysis. This presentation draws on recent research conducted by our group at the LSHTM, and supported by the Global Forum for Health Research[1].

I want first to introduce the concept of cost-effectiveness, for those of you not completely familiar with it. The essential point is a simple one: that we cannot decide on whether an intervention or programme is worth supporting unless we have information on not only its effectiveness but also its cost. Since resources are scarce, putting money into one activity is always at the expense of not doing something else. Therefore simply knowing that we have a new technology that works is not sufficient to decide to spend money on it. We must compare the costs and effects of the new technology, with the costs and effects of additional investment in other services. Thus research on the costs of an intervention is as important as research on its effectiveness (and I might add for research funders, much less costly to fund). Costs are divided by health effects to obtain a cost per unit of health effect, known as the cost-effectiveness ratio.

There is a further consideration that economic analysis can take into account. This is that diseases give rise to an economic burden on individuals and governments, and that disease reduction can therefore produce savings in resources. The simplest example is where individuals spend money on treatment of malaria, but if a mosquito net programme reduces malaria incidence, there are benefits in the form of reduced expenditure. There are also likely to be more general economic development benefits arising from malaria control.

Knowledge on the cost-effectiveness of malaria control is more advanced than knowledge on the economic burden of malaria and economic benefits of control. I am therefore going to spend only a short amount of time on economic burdens and benefits, before considering the cost-effectiveness of control measures.

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[1] Goodman C, Coleman P, Mills A (1999) The cost-effectiveness of malaria control in sub-Saharan Africa. Lancet (in press). Chima R, Goodman C, Mills A The Economic Impact of Malaria in Africa: a critical review of the evidence. Bull WHO, submitted.

The economic burden of malaria

There are very good grounds for supposing that malaria has adverse consequences for economic development. There are some key mechanisms through which this occurs. These include:

1 the detrimental impact of malaria on the ability of people to work hard, either because they themselves are sick or because their children are sick
2 the effect of malaria on child development and ability to benefit from schooling
3 the economic costs of the impact on land use, if land goes uncultivated because workers are sick
4 expenditure on treatment and prevention by households and the public health sector.

I want to say a little more about some of these.

We know that malaria affects the time and effort that households can put into production, and that the main period of transmission can coincide with peak demands for labour. There is also evidence that malaria can cause children to be absent from school. However, there are also more pernicious effects on child development and ability to benefit from education. Malaria is known to be an important cause of anaemia, epileptic convulsions, growth faltering, and neurological sequelae. These are all likely to affect children's performance at school, and we know from the literature on the economics of education that a less educated child is a less productive adult. Hence the effect of malaria on children is likely to persist into adulthood.

In terms of expenditure on treatment and prevention, sometimes substantial sums are spent by households. Figure 1 shows monthly household per capita expenditure on treatment related to malaria. Amounts range up to $4 per capita per month, and are particularly high in urban areas. Similar evidence of expenditure on goods that may offer protection against malaria and mosquitoes (Figure 2) suggests sums of up to $2 per person per month.

Figure 1:

Monthly per capita expenditure by households on malaria-related treatment

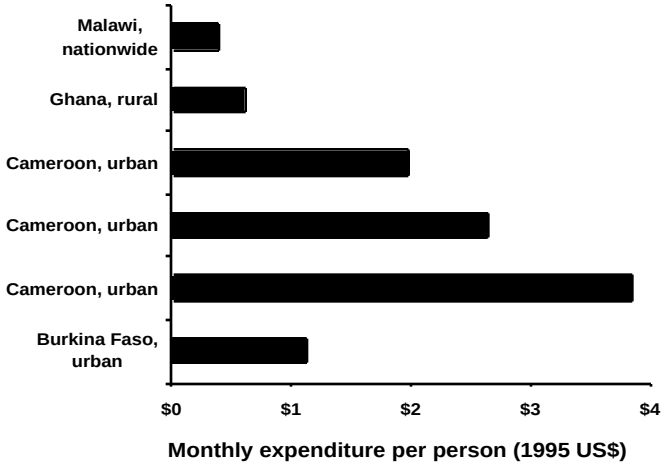
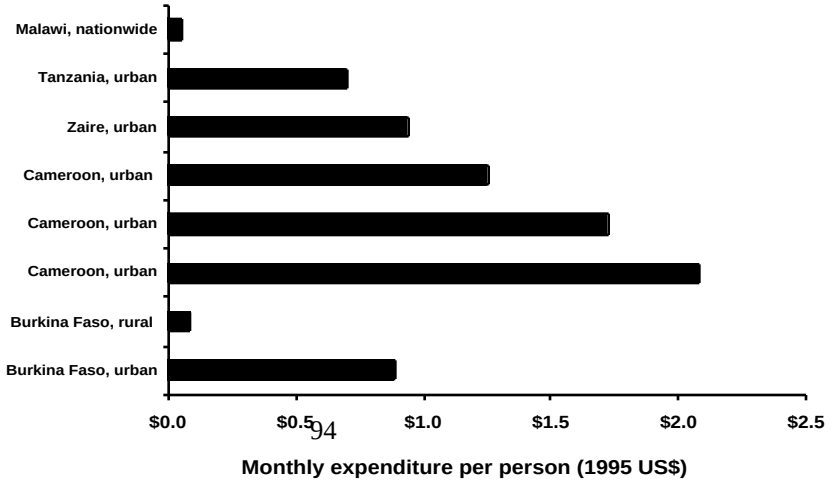


Figure 2:

Monthly per capita expenditure by households on



protection against malaria/mosquitos

The burden on the public health system is best demonstrated by evidence of the burden on peripheral health facilities. For example, around 20-40% of outpatient visits in SSA are for 'fever'[2], and suspected malaria amongst inpatients ranges from between 0.5% to 50% of admissions. Treating an outpatient for suspected malaria cost around $1 in government and mission facilities in Malawi (Ettling & McFarland 1992), and inpatient treatment for severe paediatric malaria cost $64 per admission in the Kilifi district hospital in Kenya, and $34 in the adjacent Malindi sub-district hospital (Kirigia *et al*. 1998). Kirigia *et al.* also estimated that 15% of the annual recurrent costs of inpatient care in the Kilifi district hospital, and 9% in Malindi, were absorbed by paediatric malaria admissions.

More generally, malaria may have a pervasive effect on the economic incentives, behaviour and strategies of households. Households may, for example, limit the specialisation of labour and maintain labour reserves to reduce the risk of labour shortages at key times of the year. This may protect them from catastrophic losses, but will also reduce productivity. Households may be reluctant to invest in productive activities or child schooling, again depressing productivity, especially in the longer term.

Recent work, which uses economic growth models to assess the effect of malaria prevalence on depressing economic growth rates, suggests that there are indeed likely to be pervasive effects. Work in progress by Gallup and Sachs is exploring macro-economic impact by including a measure of malaria as an explanatory variable in economic growth models (Gallup & Sachs 1998). Preliminary results suggest that countries with substantial falciparum malaria in 1965 grew 1.3% per year less over the next 25 years. This analysis controlled for other influences on growth including tropical location and life expectancy as a measure of general health. A 10% reduction in malaria over the period was associated with 0.3% higher growth per year.

These findings highlight the need to develop a more detailed understanding of the mechanisms by which malaria affects households and economies. Such research will support advocacy for malaria control. However it can also be used to target control interventions. Better information on economic impact is required to identify the population groups and regions most at risk of adverse economic effects. For example, it is remarkable that good information is lacking on the relative incidence of malaria by socio-economic group, and especially its impact on the poorest. Appropriate economic impact data could also be used to identify the interventions which make the largest contribution to reducing the economic burden. For example preventive interventions which reduce transmission levels could have a significant impact on increasing economic incentives for investment and saving.

The cost-effectiveness of malaria control interventions

I said at the start that prior to decisions on spending money on a particular intervention, it is vital to know its cost in relation to its effectiveness. A small number of cost-effectiveness studies have been done: Table 1 summarises the evidence-base. In addition, a variety of other studies have produced evidence either on costs or on effects, and Table 2 summarises the overall availability of evidence. There are some key problems in using these data to inform

[2] The proportion of these that are actually malaria will vary greatly by area and season

overall policy. In particular, country coverage is haphazard, and relates to where the main research institutions are located. Thus there is better evidence on The Gambia and Malawi, for example, than elsewhere. In addition, cost-effectiveness studies have not always been done in a way that facilitates a judgement on their relevance to other settings. For example, most studies produce what is called a single point estimate of cost-effectiveness, and undertake only limited analysis of a plausible range for the cost-effectiveness ratio.

Table 1: Number of cost-effectiveness analyses available on malaria interventions

Type of intervention	Number of cost-effectiveness studies
ITNs	**6**
Residual spraying	**1**
Prophylaxis for children	1
Antenatal prophylaxis	**3**
Improving treatment	**2**
Environmental management	**0**
Control of epidemics	**0**

Table 2: Availability of evidence for estimating costs and effectiveness

Intervention	Health Outcomes	Costs
ITNs	***	***
Residual spraying	**	*
Prophylaxis for children	*	*
Antenatal prophylaxis	**	*
Improving treatment	*	*
Environmental control	-	-
Control of epidemics	-	-

Key:

– nothing
* very limited (one or two studies)
** fair (several studies)
*** good (several studies from a variety of settings)

We have been engaged in research designed to use available data to estimate cost-effectiveness in a form useful to policy makers and programme managers and which enables operational research priorities to be identified. Because of lack of information on other interventions, those interventions we have been able to evaluate are:

- Preventing malaria in childhood (insecticide treated nets, residual spraying of houses, chemoprophylaxis)
- preventing malaria in pregnancy (chloroquine chemoprophylaxis, sulphadoxine-pyrimethamine (SP) intermittent treatment for primigravidae)
- improving treatment of uncomplicated malaria (improving compliance with drugs, improving the availability of second and third line drugs, changing the first line drug for treatment).

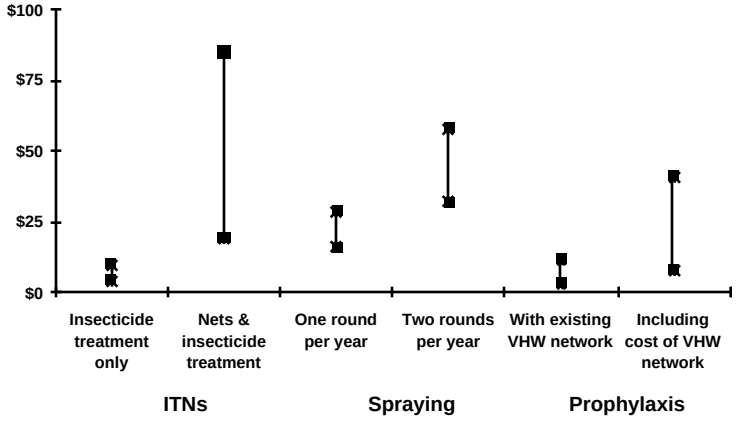
Before presenting the results, I want to highlight some key features of our methodology:

- we used a modelling approach to provide a consistent framework for the analysis of the various interventions, and to produce comparable estimates of cost-effectiveness
- we derived our data on effectiveness as far as possible from randomised controlled trials, but adjusted them to estimate operational effectiveness using compliance rates recorded in more realistic settings
- where the information allowed and when relevant to the intervention, we did separate calculations for low and high transmission areas, and perennial and seasonal transmission
- we used the disability adjusted life year as our unit of outcome: the DALY, as it is known, is a measure of health outcome which incorporates both premature death and morbidity/disability. It is useful because it enables interventions with differing effects on mortality, morbidity and disability to be compared
- since some costs such as salaries differ systematically by level of economic development, we also did separate calculations for countries in 3 income groups. In this categorisation, Tanzania, for example, is a very low income country, Cameroon a middle income country, and South Africa a higher income country
- we calculated the cost of adding the intervention to an existing delivery system, and included costs to both the government and individuals. Cost data were obtained through reviews of published and unpublished literature, and consultation with researchers and programme managers
- we used a method called probabilistic sensitivity analysis to produce cost-effectiveness ranges – this involves specifying a range and distribution for each variable in the models, and then running the models many times to generate a cost-effectiveness distribution. Summary indicators calculated were the mean and range within which 90% of the cost-effectiveness ratios fell.
- In order to interpret the results, we relied on guidelines used by WHO to interpret cost-effectiveness ratios. These guidelines state that in low income countries, an intervention is considered "highly attractive" if the cost per DALY falls below $25-30, and "attractive" if it falls below $150 (WHO 1996).

I want now to present the results. To simplify the presentation, I will show results only for a very low income country with high transmission. As I show the cost-effectiveness ranges, I will provide more detail on the specific nature of the intervention evaluated. Figure 3 shows the results for interventions to prevent malaria in childhood. The analysis of insecticide treated nets assumed treatment with the insecticide deltamethrin on a communal basis.

Figure 3: Cost-effectiveness of prevention of malaria in childhood

Two possible scenarios were considered: firstly, where nets were distributed to households as part of the programme, and secondly where treatment was arranged for existing nets. Estimates of effectiveness were drawn from the Cochrane meta-analysis of African trials, and were adjusted to account for lower net retreatment rates in operational settings.



Residual spraying calculations assumed a government-run programme and the insecticide lambda-cyhalothrin. In the absence of recent evidence on the health impact of residual spraying, it was necessary to rely on infant mortality reductions recorded during three controlled trials in the 1950s and 1960s. No health effects outside this age group or any reduction in morbidity could be included.

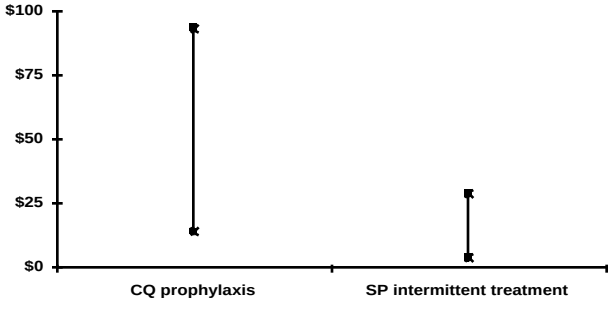
The chemoprophylaxis for children intervention consisted of the fortnightly distribution of the antimalarial, Maloprim® to children aged 6 to 59 months by village health workers under two scenarios: one where a network of volunteers existed already and one where it was necessary to establish a cadre to run the programme. Evidence on effectiveness was based on a Gambian trial which had used Maloprim, and was adjusted by realistic compliance estimates.

Figure 3 shows that all these interventions represent attractive use of resources, and highly attractive where nets already exist in communities and do not need to be purchased, and where there is an existing health worker network to give prophylaxis. An immediate reaction of some of you may be that there are a whole range of problems in implementing these interventions in practice: I do not wish to minimise these, but rather to point out that given the level of cost-effectiveness, it is worth putting in substantial effort to overcome the problems.

The intervention to prevent malaria in pregnancy consisted of two alternative drug regimens for primigravidae only: weekly chloroquine chemoprophylaxis; or two intermittent treatments with sulfadoxine-pyrimethamine. Their effectiveness drew on a meta-analysis of chemoprophylaxis which found a significant increase in the birth weight of children born to primigravidae (but not to multigravidae). The sample sizes of the studies were too small to demonstrate a significant impact on neonatal mortality, so the impact was modelled based on birth weight distributions and birth weight specific neonatal mortality rates.

Figure 4: Cost-effectiveness of prevention of malaria in pregnancy

Figure 4 shows again that this intervention is highly cost-effective, especially the regimen involving sulfadoxine-pyrimethamine. I should note that these calculations assume a certain level of resistance to the two drugs, and that re-running the calculations assuming different levels of resistance showed that the conclusions were robust to plausible resistance levels.



Three interventions to improve case management were evaluated:

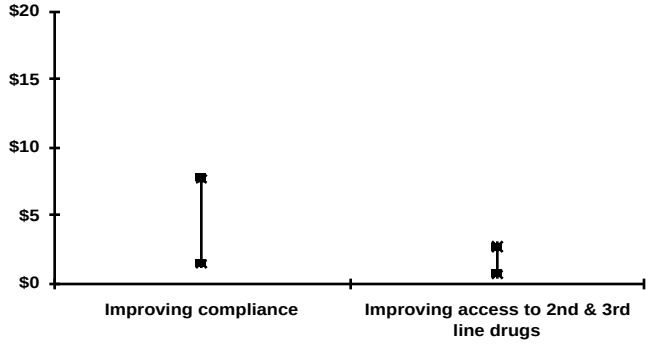
1. improving compliance with chloroquine through training of providers, health education for patients and care-takers, and the pre-packaging of chloroquine in plastic bags. These reduce the probability of failure of the first line drug, thus increasing the proportion of cases cured overall and reducing morbidity and mortality
2. improving the availability of second and third line drugs so cases of treatment failure with the first line drug, namely chloroquine, can be prescribed alternatives, namely sulfadoxine-pyrimethamine, then quinine

3. changing the first line drug for the treatment of uncomplicated malaria from a regimen where chloroquine is the first line drug, sulfadoxine-pyrimethamine the second line drug and quinine the third line, to a regimen where sulfadoxine-pyrimethamine is the first line drug, amodiaquine the second line, and quinine remains the third line.

Few evaluations of interventions to improve treatment include evidence on health outcomes, so a decision tree model was developed to translate changes in intermediate outcomes, such as compliance and drug efficacy, to final health outcomes. For those of you unfamiliar with decision tree analysis, it traces the possible paths a patient could follow who presents at an outpatient facility with suspected uncomplicated malaria. Probabilities are attached to each branch. For example, a patient with treatment failure may either remain with uncomplicated malaria, or develop severe disease. If the latter, they may or may not seek admission to hospital. Each path is traced to the final health outcomes of death, survival with neurological sequelae, or full recovery.

Figure 5 shows that the first two interventions are highly cost-effective. Indeed, the scale of the graph has been enlarged to show them clearly. Although lack of data prevented us doing similar calculations for improving treatment of severe malaria, I strongly suspect that this would be similarly cost-effective.

Figure 5: Cost-effectiveness of improving case management



We also evaluated the decision to change the first line drug. At given levels of drug resistance, a switch from chloroquine to sulfadoxine-pyrimethamine appears highly attractive. However, this static analysis ignores concerns that resistance to sulfadoxine-pyrimethamine will rapidly increase once it is widely adopted, and that affordable alternative antimalarials will not be available. Analytical methods must therefore allow for the growth of drug resistance over time, and incorporate trade-offs between higher drug costs, immediate reductions in morbidity and mortality, and potential increases in resistance to replacement drugs which could lead to higher morbidity and mortality in the future. For these reasons it is not possible to summarise the intervention in a single cost-effectiveness ratio. However, when growth in resistance is allowed for, the model suggested that it may be optimal to wait several years before switching, at the short term cost of higher morbidity and mortality. A key difficulty in undertaking this analysis is that so little is known about the growth rate of resistance over time.

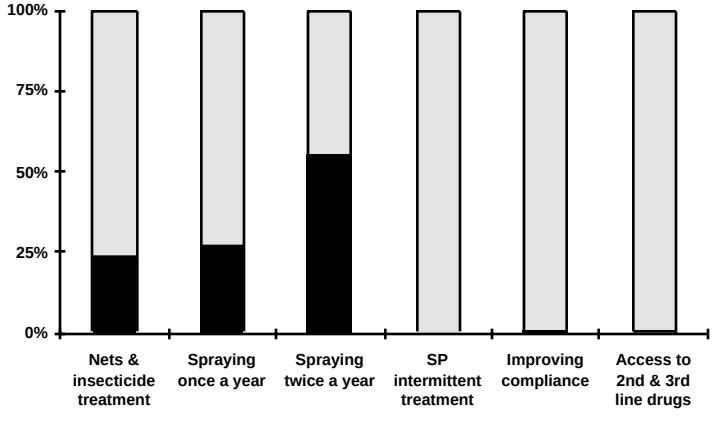
Conclusions

The central message to policy makers and programme managers from this work is that highly cost-effective interventions exist to help control malaria. There are clearly innumerable problems to be faced in putting these interventions in place and expanding their coverage, not least issues of acceptability and drug and insecticide resistance. However, effort can clearly be justified on the grounds that these interventions are just as good value for money as immunisation programmes, for example.

This analysis also highlights that the most cost-effective mix of interventions will vary from place to place. Cost-effectiveness is affected by a variety of factors, not least on the cost side the level of existing infrastructure, input prices, and the scale of activity; and on the effectiveness side epidemiological and demographic factors, and capacity to implement an effective programme. In addition, acceptability of the intervention to local people affects both costs and effectiveness. Country level analysis is thus needed to feed into decisions on country policy.

It is important to note that cost-effectiveness analysis is concerned with the unit cost of achieving a health effect. The total cost of implementing an intervention will depend on the extent of the problem to be tackled and the population coverage sought. To give an idea of the affordability of each intervention, we calculated the total cost of full coverage of the population at risk in a typical very low income country, and expressed it as a percentage of the funds available to the government for health (Figure 6). Some interventions were relatively inexpensive: prevention in pregnancy, improving compliance with treatment, and improving the availability of second and third line drugs would each absorb less than 1% of the existing budget. However achieving high coverage with an intervention to prevent childhood malaria could have an extremely high total cost. For example, full coverage of children under five with the provision and treatment of insecticide treated nets would cost the equivalent of 24% of the existing health care budget, though if insecticide treatment only were required, this would take up around 3%. The same coverage with residual spraying would be even more expensive, costing the equivalent of around 27% of the existing budget with one round per year, and 55% with two rounds.

Figure 6: Affordability to government: cost of full coverage as % of current health expenditure



In the face of many pressing coverage as % of current health expenditurepriorities and limited resources, a package of interventions which would significantly reduce the bulk of the malaria burden is evidently not affordable to very low income countries through government finance alone. While there is scope for increased private sector involvement, it is clear that the most vulnerable and impoverished groups in Africa will not be reached with effective prevention and treatment without substantial external assistance.

This analysis also has a message for malaria researchers and funders. It highlights key gaps in the research evidence required to underpin Roll Back Malaria. For several of the interventions the data are particularly poor: there is no up-to-date information on the health benefits of residual spraying; the effectiveness and costs of chemoprophylaxis for children were derived from a single study; and very few studies are available on treatment interventions. The results

of the analyses of antenatal prevention and interventions to improve treatment are dependent on extrapolations from intermediate outcomes such as birth weight and compliance to final health outcomes; these relationships have not yet been validated empirically. The lack of data prevented analysis of several potentially important interventions, including environmental management, epidemic surveillance and prevention, and interventions to improve the treatment of severe malaria. All these require attention from researchers and funders. Operational research is also vital if the cost-effective interventions are to be tailored to local circumstances and delivered equitably, efficiently and effectively.

Acknowledgements

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Kirigia, J. M., Snow, R. W., Fox-Rushby, J. & Mills, A. 1998 The cost of treating paediatric malaria admissions and the potential impact of insecticide treated mosquito nets on hospital expenditure. *Tropical Medicine and International Health* 3, 145-150.

WHO. 1996 *Investing in Health Research and Development: Report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options* Geneva: TDR/Gen/96.1.

BREAKOUT SESSIONS: ECONOMICS OF MALARIA

Programme

1. Demand for Malaria Treatment and Prevention.

Chair: Professor Anne Mills

Rapporteurs: Catherine Goodman and Omer Mensah

Report reviewers: D Filmer, C Goodman, K Hanson, O. Mensah, A Mills, P Mujinja

Aim:

- Share information on research in progress and planned.
- Suggest research agenda on economics of malaria.
- Provide the opportunity for African researchers to present work in progress or recently completed.
- Identify capacity development needs.

Content: 10-minute presentations of papers. Substantial discussion time.

1. Willingness to Pay for Insecticide Treated Bed Nets for Malaria Control: A Case of Bagamoyo Bednet Project - Phare Mujinja.
2. Willingness to Pay for Insecticide Treated Nets Before and After Implementation of ITN in a Semi-Rural District of South Mozambique - Martinho Dgedge.
3. Willingness to Pay for Insecticide-Treated Nets in 5 Nigerian Communities - Obinna E. Onwujekwe.
4. Is Money the Only Problem? Constraints to Net Ownership in Rural Tanzania - Romanus Mtung'e.
5. Availability and Affordability of Insecticide for Treating Bednets in The Gambia - Jane Rowley.

Research agenda on:

- willingness to pay
- willingness to pay methods
- determinants of demand

2. Supply Issues and Markets

Chair: Professor Anne Mills

Rapporteurs: Catherine Goodman and Omer Mensah

Economic analysis of interventions

1. Using Mathematical Tools to Predict the Economic Costs and Benefits of Malaria Control Interventions - Eve Worrall.
2. Modelling the Cost-Effectiveness of Malaria Control Interventions - Catherine Goodman.
3. A Cost Analysis of First-Line Mild Uncomplicated Malaria Treatment in the Tonga District of Mpumalanga - Justin Wilkins.

Research agenda on:

- cost-effectiveness analysis
- value of modelling approaches to CEA
- delivery strategies

Market analysis

1. Markets of Malaria Prevention and Control Commodities: Towards a Framework - Kara Hanson.
2. How can national Malaria Control Programmes in Africa act to maximise the public health utility of commercial markets in nets? The Tanzanian example and the advantages of a 'catalytic' approach - Jo Lines.
3. The social marketing of Insecticide treated nets in Tanzania; a strategy for expansion - Jane Miller.

Research agenda on:

- the operation of markets for malaria related commodities
- the best way to promote sustainable markets for products such as nets and insecticides
- the effects on the poorest of market-orientated strategies

3. Public Policy

Chair: Germano Mwabu

Rapporteurs: Catherine Goodman and Omer Mensah

1. Public economic aspects of malaria control - Deon Filmer
2. Effective malaria control: the political, economic and institutional constraints - Caroline Sergeant.
3. Impact of health care financing reforms on the management of malaria in Ghana - R. Biritwum.

Research agenda on:

- role of government in various aspects of malaria control
- political, economic and institutional constraints to effective malaria control
- effect of health sector reform on malaria control
- approaches to reform and elements of reform that best support effective malaria control

Summary Report: Economics of Malaria

Introduction

Whilst a number of scattered studies have been done on the economics of malaria in Africa in recent years, this was the first time that economists working on African malaria had been brought together, and the conference thus represented a landmark in the development of a group of researchers creating a body of knowledge on this topic. The identification of economics as a session topic was greatly appreciated, and enabled much needed interaction between economists and control staff.

The presentations and discussions were organised into three sessions on firstly the demand for malaria prevention and treatment, secondly supply issues and markets, and thirdly public policy. The sessions were very well attended, and featured a number of presentations by African economists who are keen to continue to work in this field.

1. Demand for Malaria Treatment and Prevention

This area covers the consumers' perspective – why, where and how people seek prevention and treatment? Key questions considered were:

- What methodological approaches can be used to obtain information?
- What have we learnt about factors influencing demand?

There are two ways of analysing demand: firstly studying actual purchases, and secondly undertaking Willingness-To-Pay (WTP) surveys, where potential customers are asked hypothetical questions about the amount they would be willing to pay for commodities. As some malaria control tools, such as nets and insecticides, are relatively new products in some communities, the WTP method has been advocated to predict and analyse potential demand.

Several studies were presented on the demand for nets and insecticides in Africa which had been designed to test the methodology of WTP studies. The researchers raised several reasons why WTP estimates were not always good predictors of actual purchase, including growth in public awareness about nets between the survey and time of sale, and strategic behaviour by respondents who were trying to influence the price set by the programme. In view of these problems, further work is needed on assessing both actual and potential demand.

Several studies found a clear relationship between socio-economic status and WTP for nets, and households clearly face many other competing demands on their income. Whether a price is charged and the level of this price has implications for affordability for the poor. In addition, as the price set affects coverage levels, it may also influence the effectiveness of interventions if they depend significantly on a mass killing effect and therefore need to have relatively high coverage to have a major impact on health.

Other factors highlighted in discussions as affecting demand and meriting further investigation included:

- Seasonality of the availability of income
- Low levels of awareness about the transmission of malaria and unfamiliarity with the intervention
- Gender roles in the household – in some settings women were more aware of the benefits of interventions, but men controlled expenditure for large items such as nets

· Accessibility and availability of products – in some cases this was a crucial factor for both nets and insecticide.

Analyses of this type can feed into the design of interventions. Further work is needed to explore the scope for several strategies including:

· Use of credit, and potential for linking with existing community micro-credit schemes
· Seasonal payments, which allow people to pay at times of the year when income levels are highest, such as the harvest
· Targeting subsidies on the most vulnerable groups, and thinking about issues related to "leakage" to less needy groups
· Targeting messages to household members responsible for expenditure decisions
· Strategic points for net distribution and sales to stimulate potential demand.

Analyses have to date focused mainly on ITNs. More work is also needed on the demand for other preventive commodities, such as insecticide retreatment products and services, and for curative services.

Conducted at a relatively low cost, the set of WTP studies demonstrated the value of a targeted effort to answer specific questions through a cluster of studies in different countries. These studies need to be finalised and made available more widely. The potential for other areas to benefit from such targeted research needs to be considered.

2. Supply Issues and Markets

This session had two themes: A) cost-effectiveness of interventions and B) analysis of markets.

A. Cost-effectiveness of Interventions. Cost-effectiveness analysis is an important tool for decisions on resource allocation, but very few cost-effectiveness analyses on malaria control are currently available. This has necessitated the use of modelling techniques to estimate the cost-effectiveness of interventions. Several papers were presented on this topic, raising a number of points :

· Highly cost-effective interventions exist to help control malaria; there are clearly many problems in their implementation, but effort can be justified on the grounds that they are good value for money.

· The most cost-effective mix of interventions will vary from place to place, depending on the level of existing infrastructure, input prices, the scale of activity, epidemiological and demographic factors, acceptability to local people, and capacity to implement an effective programme.

· There is a paucity of information on costs and effectiveness in operational settings (as opposed to trial conditions). A particularly important example is the lack of information on the relationship between the coverage of ITN projects and the existence of a mass effect, meaning that the effectiveness of ITN projects at the low levels of coverage often found in operational settings is not known.

· Estimates are not available of the cost-effectiveness of a mix of interventions implemented simultaneously. For example, the same population could use ITNs and chemo-prophylaxis, but information is available only on the cost and effects of each intervention implemented alone.

· It is important to consider how the cost-effectiveness of interventions will change at different scales: the benefits of economies of scale may be reaped, but it is also possible that diminishing returns will set in, increasing the importance of using a mix of interventions.
· More work is needed on comparing the cost-effectiveness of alternative delivery strategies for a given intervention to maximise the efficiency of resource use.
· In modeling cost-effectiveness, uncertainty about parameter estimates is a major concern. Cost-effectiveness studies should identify the key variables causing that uncertainty, so that research can be targeted at these issues.
· Research is needed on the cost-effectiveness of interventions in areas of unstable transmission.

B. Analysis of markets. There is a growing recognition that the private sector is an important source of prevention and treatment, and that the public and private sectors influence one another. However, relatively little is known about the operation of the private sector, or how public policy can be used to improve its performance in achieving public health goals. A general theme of the session was that to take into consideration market failures and design appropriate interventions it was necessary to take a market perspective. This involves developing an understanding of household behaviour in relation to purchase, and supplier behaviour in relation to provision. Several presentations focused on how best to develop markets for ITNs, raising a number of points:

· There are likely to be problems in scaling up subsidised programmes; as publicly run programmes are unlikely to be more efficient than the private sector, a subsidy will need to be maintained which will be unaffordable on a national scale.
· Strategies to expand ITN coverage through the commercial sector must balance the development of a sustainable and competitive commercial sector with issues of equity of access to goods of public health importance.
· Strategies such as product differentiation should be explored to investigate the potential to effectively target subsidies on those who cannot pay the market price.
· There is a risk that the promotion of subsidised products will crowd out commercial initiatives, and so impede the development of private markets. On the other hand, subsidised promotion may lead to a 'halo effect', meaning that commercial market development is stimulated both within and outside the project area.
· The effect of branding on the market structure must be considered.
· The markets for commodities, such as nets and insecticide, are very different, and therefore their promotion may require quite different approaches.
· Further thought needs to be given to markets for other commodities, particularly drugs. This is very high priority given the substantial size of private drugs markets.
· There is a need for further development of tools for assessing both market supply and demand.

3. Public Policy

There is a strong economic rationale for some kinds of public intervention in malaria control due to the presence of several market failures (including public goods, externalities and asymmetric information), as well as equity concerns.

However, there may also be government failures which need to be addressed. There are a range of social, economic, institutional and political constraints to the implementation of

effective malaria control. Financing mechanisms are weak, and personnel often lack incentives to perform well. Ministers may be unaware of what is going on at the grass roots, while political commitment is often lacking at the district level and below, and the role of local government is rarely considered.

Successful implementation of control strategies will be dependent on an understanding of the constraints faced and a serious attempt to address key problems. This will require input from a range of disciplines, including political science, to explore the influences on resource allocation and the problems of getting evidence into action.

A key question is 'How should governments intervene?' This could take a range of forms, incorporating provision, financing and regulation. Several points were raised under these themes.

- Provision

We need to consider how malaria interventions can be linked and integrated with existing services for other health problems. The appropriate mix of public and private providers must be explored, and the potential interactions between the private and public sectors considered. Work is needed on approaches to improve the efficiency and quality of public sector health services.

- Financing

Cost-recovery should be assessed in terms of its impact on the behaviour of providers, and on its implications for efficiency, equity, access and quality. More sophisticated analysis is needed of incentives facing public and private providers, and how these affect their behaviour.

- Regulation

This is a key research priority – the roles of professional bodies, government agencies and the community need to be explored.

Research Priorities

In the time available it was not possible to consider and agree on a comprehensive research agenda, but a number of key priorities for health economics research were highlighted.

1. The economic burden of malaria

· Link between poverty and malaria

2. Public policy

· Issues of regulation (government, professional bodies,etc.)
· The implications of a range of cost-recovery strategies for cost, quality and access
· Political science research on political and institutional constraints to policy implementation

3. Demand

· Analysis of the predictive value of alternative elicitation mechanisms for WTP studies, and the impact of information provided or methods used on responses
· Studies of consumer preferences and allocation of household resources

4. Analysis of supply issues and markets

- Development of a framework which will assist thinking about the role and behaviour of markets for malaria related commodities
- Evaluation of behavioral and market impact of different types of interventions

5. Cost-effectiveness analysis

- How should regional variations in epidemiology be used in the design of control interventions? What level of detail on risk variations is required to cost-effectively target control measures? For example some policies would be more appropriately applied nation-wide, but others might be left to districts to decide. Collaboration between epidemiologists and economists will be essential to address this issue.
- Generation of information on the costs and effects of interventions in operational settings
- Analysis of the cost-effectiveness of a package of interventions
- Comparison of alternative delivery strategies for interventions (e.g. different methods of net distribution and treatment)
- Analysis of particular interventions – drug regimens (in particular combination therapies), diagnostics, herbal remedies, control strategies in areas of unstable malaria

6. Design of new malaria control tools, such as drug therapies, vaccines and diagnostics

- Social science and economics should be used to influence the design of new tools, and not just brought in to help deliver interventions once developed.

In addition it was highlighted that social science disciplines other than economics have a vital contribution to make to Roll Back Malaria. In particular, an understanding of people's social and economic behaviour is essential for the design of appropriate interventions. It was concluded that future meetings should include the opportunity for other social scientists to have similar discussions.

Implication of Research Results for Treatment or Control of Malaria

- Market failures justify some kinds of public intervention, but this may take several forms including provision, financing, regulation and information provision.
- The design of interventions by governments and NGOs should take a market perspective, considering the impact of strategies on the actual and potential supply in the public and private sectors.
- The effect of cost-recovery mechanisms on the behaviour of providers and households must be carefully considered.
- The design of delivery strategies should be based on a detailed understanding of the binding constraints on purchases, and a recognition that these are not purely monetary.
- Highly cost-effective interventions are available for both the prevention and treatment of malaria; the most cost-effective package in a particular setting will vary depending on both epidemiological and socio-economic conditions
- There is an important role for cost-effectiveness considerations in the planning process at national and local levels.

Strengthening Links between Research and Control

To date the contribution of economic analysis to the design of malaria control strategies has been limited, partly because the body of work available is still quite small, and partly due to problems of communication.

There is a need for an 'interpreter' to translate the evidence provided by researchers into terms that can be easily understood and utilised by control personnel and decision makers. This will require greater dissemination efforts on the part of researchers, and also capacity building among members of the control community. A specific mechanism or unit may be required to interpret and transfer information.

There is also a need for greater links between researchers from the social science and science fields.

Identified Research Capacity Needs (Human Resources)

There is a dearth of African economists working in the health field for several reasons:

- Health economics is a relatively new field of economics, and most African economists are not trained in this area.
- Poor remuneration and conditions of service cause a brain-drain of economists away from the public sector, where most health economics posts are based, and some of the best health economists are attracted away to work for international agencies.
- The low number of health economists and the lack of understanding and appreciation of the role of economics among other health personnel, make it difficult for health economists to work effectively.

It was also noted that the health economists who are available are often not well utilised and are not involved in the policy making process and the design of programmes.

Several approaches were identified to develop health economics capacity:

- The WTP studies presented were excellent evidence of the value of a focussed approach to developing knowledge on a particular topic, involving a call for proposals, a workshop to help develop proposals, and support to researchers. Such research is not costly to do, and has high pay-offs in terms of knowledge generation and capacity development
- Small workshops are very effective for training and networking
- A network of African health economists working on malaria should be encouraged
- African health economists need improved access to information on current research, and obtaining grants
- The curricula of graduate economics courses is often inappropriate for the applied work health economists undertake in Africa
- Resources are required to upgrade the skills of middle level health economists, so they can perform a more senior role.

It is not only health economists who are lacking – there are also very few trained personnel in other social science fields and this issue also needs to be addressed.

HEALTH INFORMATION SYSTEMS

Plenary Presentations

Information for Malaria Control in Africa : Are We Ready?
Don de Savigny
The MARA/ARMA Project – Theory and Practice.
Marlies Craig
MARA and the Kenya Country Experience.
Judy Omumbo

Breakout sessions

Programme

1. Data Needs for Malaria Control I
2. Data Needs for Malaria Control II
3. Epidemic Preparedness and Data Needs.

Summary Report

PLENARY PRESENTATIONS

Information For Malaria Control In Africa : Are We Ready?

Don de Savigny, Tanzania Ministry of Health, Dar es Salaam, Tanzania

First, I wish to congratulate the organizers of the MIM Malaria Congress for putting the issue of Information and Communication so prominently on its agenda. Of the 30 plus sessions this week, at least 8 are fully or largely dedicated to health information systems and connectivity in support of malaria control. This is highly refreshing for a disease specific conference and I hope we can all make best advantage of this rare opportunity. I also want to thank the organizers for inviting me to tackle this topic and to be provocative. But from the outset, I must also warn you that I am not an information systems specialist. Like most here, I am a health professional working in Africa and I approach the subject from that perspective. And like most of us, whether coming from malaria research or malaria control, we must be interested in evidence and information on which to base the way forward and to monitor our progress. So I hope that what I have to say will have resonance with many of you.

In public health there are three things that we always complain of not having enough

- The first complaint is that there is never enough **time** . The clock is always ticking. Our most frequently used measures of health and disease are time based, be they time denominated epidemiologic rates or more recently, DALYs, Years of Life Lost, or Years Lived with Disability. For those focussed on malaria, even if we take the lower estimates of malaria mortality in Africa such as those in Murray and Lopez' Global Burden of Disease Analysis, or Bob Snow's more recent estimates of malaria mortality in the current issue of Parasitology Today, still over 10,000 Africans, mainly children and pregnant women, will die due to malaria during the 4 days of this MIM Conference. Time will always be against us.

- The second complaint is that there are never enough **resources** . The magnitude of the burden of disease in the world everywhere, but especially Africa, always outstrips available resources to respond adequately. Resources are always finite and constrained. Choices must be made. But more and more, these choices are being made on the basis of evidence and information rather than in the past where priorities have been set largely on the basis of common sense, albeit often poorly informed common sense, tempered by inertia, by last year's budget, by last year's epidemic, by donor paradigms, by special interest groups, by politics, and by funding opportunities rather than program needs. When resources are inadequate, allocation decisions must be supported by information and evidence.

- The third complaint is that we never have enough **information** . At least the information we need. And this is the issue that I have been asked to deal with during this half hour.

Of these three deficiencies: time; resources; and information, time will always be against us; and resources will always be constrained, but information could be different. We are on an exciting threshold. The ease and pace at which we can capture, store, manipulate, and

communicate information is accelerating at a phenomenal rate. Unlike the costs of new anti-malarial drugs (and just about everything else in life), the real costs of managing and communicating information are actually dropping, and dropping fast. There are few things that have decreased in price as steadily and dramatically as the cost of storing a megabyte of information on our desktop. This has dropped about 50% per year, every year, over the past 15 years. On the information sharing front, at least for the research side of the malaria battle, e-mail can now reach field research settings such as Navrongo, Ifakara, Kilifi and many others. Several Ministries of Health in Africa already maintain their own Web Sites. For some of us there is already information overload. But is it the information we need to do the job at hand? To roll back malaria?

So, I am not going to talk about the many, still under-exploited opportunities that Information Technologies bring us. Instead, I would like to focus on the information itself, the actual sources of information for decision making.

This Conference bears witness to the fact that there is now a high level of political will to deal with malaria at the international level. We have MIM. We have Roll Back Malaria. We have the African Initiative for Malaria. We have a growing number of African networks against malaria (MARA/ARMA, EANMAT, INDEPTH to name a few). But we still do not have the necessary political will to Roll Back Malaria at the National, District, and Community levels in much of Africa.

What are the information needs to turn that corner? To mount a societal response to malaria proportional to the magnitude of the problem. What information is available? Is it what we need? What is missing? What are the new opportunities for information relevant to malaria control on the near horizon?

I will try to tackle this in two parts: the first focussing on what data sources we have now for evidence-based planning for malaria control; the second focussing on what information we need to measure our progress in reducing the burden of malaria.

1. Available Conventional Sources of Information for Malaria Control

There is not time to review all conventional sources of information for malaria control. So I would like to highlight only those that are available in the absence of a malaria control program. Where specific malaria control programs are already running well, their internal information systems are usually sufficient. But for most of Africa where integrated malaria control strategies are just taking off, information needs are more acute.

Conventional Sources of Information for Malaria Control

- **Routine Malaria Control Program Data**
  - **Vector Control**
  - **Active & Passive Case Finding**
- **Routine Health Services Data**
  - **HMIS**
  - **Standardized Hospital Reports**
- **Research**
  - **Survey Data**
    - **DHS**
    - **Community & Household Surveys**
    - **Health Facility Surveys**
    - **Rapid Appraisal and Needs Assessment Exercises**
  - **Intervention Trials**

1.1 Routine Health Services Data

1.1.1 HMIS

Let me start with the most commonly accessible information for the health system. This traditionally comes from the system's own health facilities. In the past this took the form of routine annual reports from health facilities and it was implicitly assumed to reflect the state of the health problems of the population. More recently, many countries have made efforts to systematize the collection and use of health facility data. They do this by applying health informatics to develop a Health Management Information System reaching down to the peripheral health facility level. The general purpose of such systems is to enhance quality of care, facilitate accountability, and assist cost containment. They usually do so by applying a hierarchy of:

a. Transaction Processing at the Facility and District levels, feeding into :
b. Management Information System at the Regional and National Level; followed by:
c. Decision Support back to District and Facility Level

Health Management Information Systems
HMIS

- **HMIS applies Health Informatics to:**
  - **enhance quality of care**
  - **facilitate accountability**
  - **assist cost containment**
- **Through a cycle of:**
  - **Transaction processing at Facility and District Levels**
  - **Management Information System at Regional and National Levels**
  - **Decision Support back to District and Facility Level**

Unfortunately most of the energies of HMIS go into transaction processing, rather less into the Management Information System, and least into the Decision Support back to the periphery. We see volumes of forms filled at facility level logging attendances, diagnoses, prescriptions, follow-ups, and referrals. These transactions are fed up the line to District, regional and national levels where at each stage, they are aggregated and collapsed into summary statistics. Yet very little comes back to the Districts, and virtually nothing comes back to the thousands of health facilities who continue generating information daily. In addition, the HMIS data are often incomplete due to under-reporting from HMIS facilities, and non-reporting from private and traditional facilities.

Malaria at Facility Based HMIS
National Statistics for Tanzania

- **MALARIA is:**
  - **Leading Case for < 5 admissions 49%**

Malaria at Facility Based HMIS for Morogoro, Tanzania

District Statistics

- **Malaria is:**
  - **Leading cause of health service attendance**
  - **30% of attendances (285,037 in 1996)**

But there is a more serious deficiency in HMIS data sources. Even if the HMIS cycle were to be fully functional, the utility of facility based data for estimating population health and monitoring progress is highly questionable. Such data are easily biased by the quality of services; the availability of drugs and supplies; the performance of health workers; the physical and social access of the population; the local mix of governmental, non-governmental,

traditional, and private health services; user fees and other consumer costs; and most importantly, the health seeking behaviours of households. But is this a problem for malaria data?

Health facility data in Africa often cite "30% of out-patient attendances are due to malaria". But given the chronic under-support of malaria control across Africa, such data are evidently of limited practical value and certainly have not provided sufficient lobbying clout for Program Managers to set priorities or compete for resources, either at the National or local levels.

Despite malaria's dominance in the HMIS statistics, the District Health Plan priorities in this illustration failed to mention malaria, although they did specify resources for 11 other diseases including dental caries and hepatitis B. The District response to malaria defaulted passively to the anti-malarial content of the Essential Drug Kit, which amounted to only 5% of the intervention budget of the District. I suspect the same is true across most Districts of Africa, at least those fortunate enough to have an essential drug program.
And as for monitoring change in health status, can we really use facility based statistics? How do we interpret an increase in attendance? Is it due to improved quality and utilization of services, or due to an increase in community disease burden.

1.1.2 Standardized Hospital Record Reports

Another source of data is Standardized Hospital Reports. For severe and complicated malaria, hospital admission data may be better than routine peripheral HMIS data. Certainly changes in hospitalisation over time, numbers of blood transfusions conducted, and case-fatality rates should indicate changes in severe disease patterns in a community. Age-patterns of severe disease may provide insights into locally acquired immunity patterns. Seasonal patterns of severe disease can indicate opportune times for intervention. These data are available, although subject to some degree to the same biases as routine health service data. But there are few examples of the routine use of hospital data for planning and designing interventions. Perhaps standardized reporting from sentinel hospitals could go far to supplementing an HMIS with more relevant burden of disease information.

On the whole, it is very difficult to determine the costs of a comprehensive, system wide, HMIS, just as it is difficult to determine the benefits. However the costs are substantial because large numbers of facilities and event transactions are involved, and the benefits, at least for understanding the community impact and dynamics of malaria and other diseases, are marginal. Could some of the effort and cost of generating facility data every where be re-directed to collecting more relevant, higher quality data in sentinel sites to be shared appropriately? One idea might be to strip down HMIS only to indicators required to manage that facility efficiently and re-allocate the freed resources to something else. I will come back to what that something else could be later.

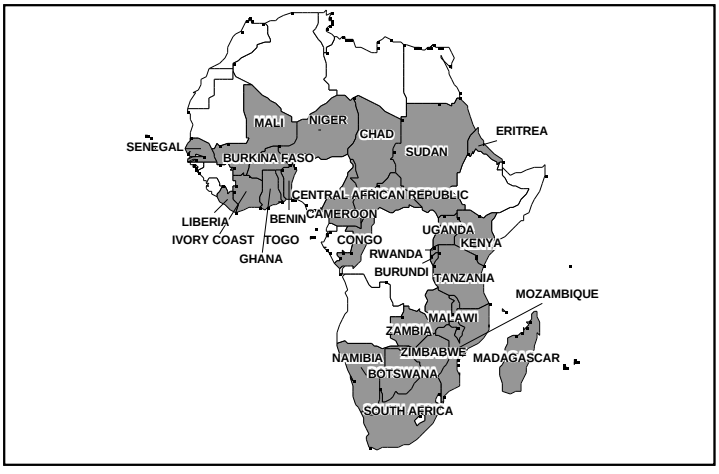
In any case, much work is required to examine the real value of HMIS data for District-level planning and impact assessment.

1.2 Research Data

1.2.1 Survey Data

The next commonly available source of information for malaria control falls under the research heading. These have traditionally come from cross sectional survey data, of which there are various sources.

Demographic and Health Surveys in Africa
29 Countries by 1999



National Demographic and Health Surveys (DHS)

National demographic and health surveys are now conducted every two years in 29 countries in Africa. These are routinely conducted on large nationally representative samples. For example, the last DHS survey in Tanzania involved 8,000 women. However samples are usually too small to allow sub-regional analysis. This is a limitation since most health reforms are decentralizing decision making to the District level at which the national DHS sample is too dilute. But the main limitation of the DHS data for the focus on mortality is that they employ indirect methods, and thus reflect the mortality pattern in the past, on average 3-5 years ago, but do not reflect contemporary burdens and impacts. Nevertheless, over time, the DHS can provide a broad picture of trends in infant and childhood mortality. But on the knowledge, attitudes and practice side, the DHS surveys offer abundant opportunities to conduct nationally and regionally representative polls of behaviours. DHS surveys often contain elaborate questions on family planning practices, respiratory diseases, diarrhoea management, etc. but have only superficial questions if any dealing with malaria, Recently, a more detailed DHS survey module on malaria is under-development. Should we, as a malaria community be influencing sampling and questions within national DHS survey instruments? For example, it would be relatively easy to develop questions which elucidate trends in bednet ownership, knowledge of net treatment benefits, source of anti-malarials, etc..

Cross Sectional Household Behaviour Surveys (impact surveys)

I now turn to non-DHS household surveys. HMIS style Information systems usually ignore health seeking behaviour and I will illustrate the consequences of that shortly. However, standardized, stratified, population proportional, cluster sample survey methods and instruments have recently been developed for the IMCI package which illuminate many important aspects of household health seeking behaviour in relation to childhood illnesses including malaria, and malaria preventive practices at home such as ITNs. These are best conducted as repeated cross-sectional surveys every few years in strategic locations where impact and trends need to be assessed. The cost is approximately 10,000 USD per survey and thus they are not for routine surveillance or HMIS.

Health Facility Multi-indicator (process surveys)

Based on the UNICEF surveys, similar cross-sectional surveys are being developed to document process change at health facility level for IMCI. These can be conducted in lock step with the Household Behaviour Surveys at marginal extra cost.

1.2.2 Intervention Trials

Still under the research heading, one of the most informative sources of data we have for malaria in Africa has come from demographic surveillance (DSS) mounted by the research community to test intervention efficacy for mortality reduction. Beyond providing objective evidence of intervention efficacy, these systems provide deep and unique sources of information on burden of disease. Just as intervention research in the form of removing the mythical Broad Street pump handle in London in the 1830's taught us much about the epidemiology of cholera, so too has the intervention research in the form of randomised field trials of insecticide treated nets in Africa in the 1990's taught us much about the epidemiology of malaria. One result has been that the direct and indirect burden of malaria was shown to be much higher than expected. Almost all prior estimates placed malaria at 10% of under five mortality, yet the ITNs prevented 20 - 30% and in some settings even more of the under five mortality. This has gone far to re-shape our appreciation of the importance of preventing malaria. However, well designed intervention trials of sufficient size to document mortality are few and far between and cannot be counted upon to contribute routinely to national information systems.

1.2.3 Rapid Needs Assessment Exercises

Finally under the research heading, there are the needs assessments and situation analyses for malaria control. These have tended to be quick, often ad hoc, in and out exercises which collate but rarely produce new information. However, given the paucity of reliable malaria data at the national, district and community levels, Roll Back Malaria is developing a tool kit for a complete needs assessment. This assessment can be conducted within the space of a few months to assemble systematically all the necessary information to determine the scope and needs for integrated malaria control. This tool is currently being piloted but is an innovation that may prove very useful to mobilize both the political will and resources at national and sub-national levels. Those interested in this can subscribe to an active list serve sharing the methodology.

So, summing up the conventional sources of information for malaria control, we find that all the approaches have important deficits. What we need to do is avoid the bias and low quality of facility based data; avoid the lack of District specificity and contemporary relevance of the DHS burden data; and avoid the patchiness and low coverage of survey data, research trial data, and rapid assessments.

2. Emerging Sources of Information for Malaria Control

So what new sources of information could provide timely data of sufficient coverage and quality to advocate for, plan and allocate malaria control resources and to monitor progress in averting the mortality and morbidity associated with malaria? Here I would like to highlight just two new areas in which international networks have emerged very recently.

2.1 Spatial and Environmental Information Systems.

The first of these can be collected under the heading of Spatial and Environmental Information Systems. These information systems include the use of Geographic Information Systems (GIS) to map populations at risk in relation to their health risks, their health services, and their health programs as exemplified by the work of Health Map at WHO.

There is also the work of MalSat, NASA, and MARA / ARMA and others to harness satellite remote sensing data and other climate data in the service of malaria epidemic prediction in the highlands and other areas of unstable malaria in Africa.

Finally, there is the malaria specific work of the MARA / ARMA collaboration which seeks to map malaria transmission risk down to 5 km resolution across all of Africa. It is also developing a continental, spatial database of all pertinent malaria indices on burden of malaria, transmission risk, entomology, drug and insecticide resistance, etc. As an example, here is one MARA risk map for Tanzania illustrating the kind of heterogeneity that exists, even at the sub-District level. We need to examine how the availability of such new perspectives on malaria will influence malaria advocacy, resources and programs at National and sub-national levels for malaria control. Since you will hearing more about MARA later in this session I will not go into further detail.

Emerging Sources of Information for Malaria Control

- **Spatial and Environmental Information Systems**
  - **Health Program and Population Mapping**
  - **Satellite Remote Sensing for Epidemic Forecasting**
  - **GIS Modeling and Malaria Risk Mapping**
- **Sentinel Demographic Surveillance Systems**
  - **Community based burden of disease and trends**

Instead I will focus on the second potentially emerging source of information for malaria control, the idea of sentinel demographic surveillance for mortality and other indicators.

2.2 Sentinel Surveillance Data

First, why mortality? According to DALY estimates, malaria is one of the first and largest components of Africa's burden of disease. 90% of the malaria DALY in Africa is contributed by premature mortality as Years of Life Lost, the YLL component. Only 10% of the malaria DALY is years lived with disability or YLDs. Even so, malaria is the fourth ranked cause of disability or YLD's in Africa, such is the magnitude of the problem. Interventions that prevent malaria mortality also prevent malaria morbidity. Indeed Christian Lengeler's Cochrane meta-analysis of randomized controlled trials concludes that ITNs reduce overall child mortality by 18% and morbidity by 48%. Since 90% of the malaria DALY is premature mortality, we must measure mortality to assess properly the effectiveness of our strategies. The problem is that in Africa, vital event registration or cause of death data in any routine information system is rare. However, as we have seen, Demographic Surveillance Systems have been used to measure mortality efficacy in trials. Can the same DSS approach be used to influence priority setting and measure effectiveness in real life programming? Perhaps yes.

Here is an example of a Tanzanian District which, in 1996 had a health facility within 5 km of 85% of its population, was allocating 5% of its budget to malaria, was treating over a quarter of a million malaria cases per year and thought it was on top of the malaria problem, at least according to its facility-based HMIS. Then a District Demographic Surveillance System (a DSS) was introduced through a DFID funded Morbidity and Mortality Project which revealed a completely new and disturbing picture of the real burden of disease as experienced by the community.

Community Based Burden of Disease Data - Insights from Sentinel Demographic Surveillance (DSS)

- ***Although 85% of households are within 5 km of a health facility…***
- **83% of all deaths occur at home**
- **84% of <5 deaths occur at home**
- **30% of total mortality burden is due to malaria**
- **45% of <5 mortality burden is due to malaria**
- **46% of deaths at home occur without prior health facility contact**
- **90% of deaths due to *acute febrile illness with seizure* occur at home**
  - ***Source: Tanzania Ministry of Health and AMMP Team, 1997.***

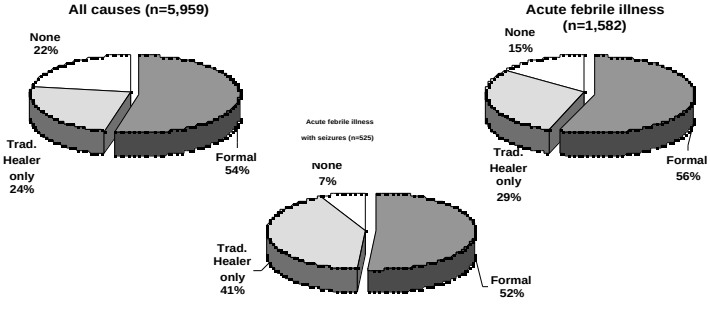
It showed that:

- 83% of all deaths occurred at home, including child deaths and were not counted in any HMIS
- 30 % of the total, and 45% of the child mortality burden was due to malaria

But more disturbingly, despite high facility attendance:

- 46% of all deaths, including malaria deaths, occurred without prior contact with a health facility
- 90% of child deaths due to acute febrile illness with seizure occurred at home.

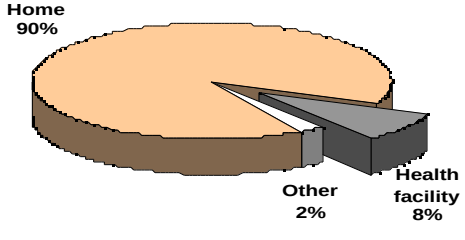
Contact with Formal Health Facilities in the Illness Leading to Death, Morogoro (R), 1992-1995 (all ages)



Based on: "The Policy Implications of Adult Morbidity & Mortality: End of Phase 1 Report" (1997) Tanzania Ministry of Health & AMMP Team, Dares Salaam.

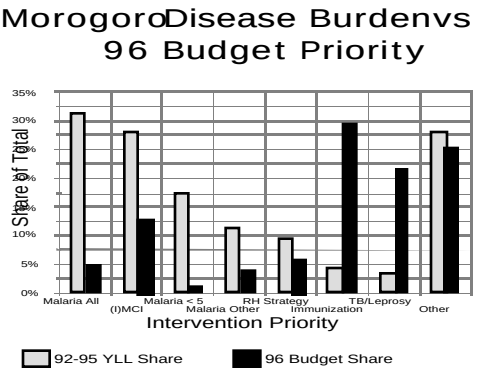
The District was shocked by 1) the degree of mortality outside the system, and 2) the degree of under-utilization of its health services for severe and complicated malaria (despite high coverage and high attendances for simple malaria). As one Ministry official put it, "*our facility based HMIS only showed us the nose of the hippo that was hidden beneath the water*".

Place of Death in Children Under 5 years from Acute Febrile Illness with Seizures Morogoro (R), 1992-1995

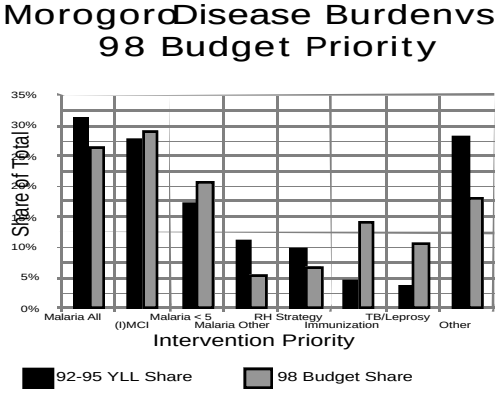


Based on: "The Policy Implications of Adult Morbidity & Mortality: End of Phase 1 Report" (1997) Tanzania Ministry of Health & AMMP Team, Dares Salaam.

What was the District response to this new appreciation from a community based DSS information system?



Unlike previously available HMIS attendance data which indicated ineffectively that malaria was a top priority, the policy and advocacy influence of these community based mortality statistics was swift. As you can see in these comparisons between 1996 and 1998, there was 5-fold increase in the share of resources directed to malaria control and a 20-fold increase in the share of resources for malaria control for children under 5. The District adopted and introduced IMCI in all its health facilities and now promotes social marketing of ITNs. Malaria is now, for the first time, given a prominence consistent with its disease burden in District Health Plans. The District DSS continues and will be used to document how these investments and strategies operate to reduce the burden of disease.



So what is a Demographic Surveillance System and how much does it cost?

A typical DSS is simply a geographically-defined, population, usually in the order of 40 to 100,000 people in which a longitudinal surveillance system documents all births, deaths, and migrations. It does so by conducting an initial census followed by re-enumeration up-date rounds at frequent intervals, at least annually if not quarterly, to determine the denominator at risk, especially young children. At the same time, a parallel system of community key respondents continually identify the numerator vital events of births and deaths. All deaths are followed up by a surveillance system supervisor who conducts a verbal autopsy to ascertain the cause of death. DSS systems have rigorous supervisory, quality control and data management systems in order to link events in the numerator to the population in the denominator. A single DSS in a rural African sample population of 100,000 will document cause and prior health seeking behaviour in an average of about 5 deaths per day. Unfortunately many of these deaths will be due to malaria.

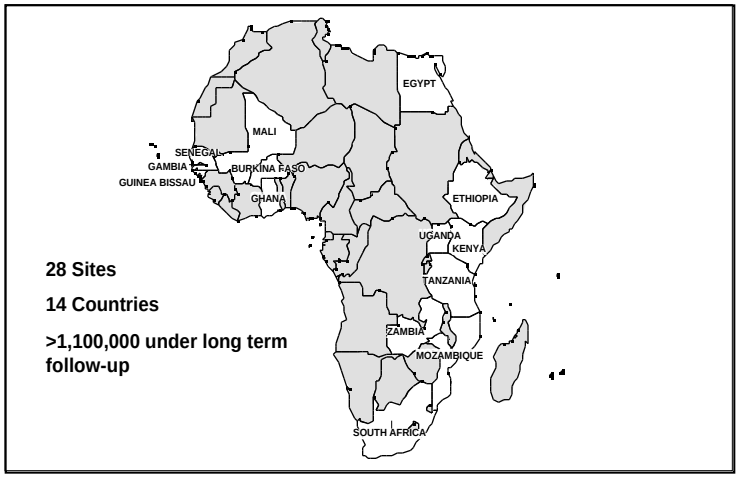
DSS: What is it?

- **Demographic Surveillance System**
  - **A geographically-defined population under continuous demographic monitoring with timely production of data on all births, deaths, and migrations (INDEPTH, 1998)**
- **How does it work?**
  - **enumeration of denominator population by repeated household visits at regular intervals**
  - **continuous reporting of numerator vital events by community key respondents**
  - **cause of death determined by verbal autopsy**
  - **rigorous supervisory, quality control, and data management systems**
  - **Sentinel DSS annual cost estimated at < $0.03 per capita**

How much does all this cost? To run six such DSS systems in a large country like Tanzania and using a stratification to distribute annual DSS results to Districts represented by their sentinel will cost less than 3 US cents per capita per year with present methods. UNICEF is working on a variation of village registers for vital event registration that might lower the costs of DSS even further.

Because DSS provides quality data on household burdens of disease and a platform for a wide range of health, social, economic and behavioural analyses that can not be obtained in any other way, there has been an upsurge in DSS applications in recent years. In recognition of this, over 40 DSS field sites in the developing world have recently created a collaborative international network called INDEPTH. Its purpose is to harness the full potential of such sites, increase their technical efficiency, lower the costs of the methods, and maximize the policy influence of the information generated. In Africa, there are already 14 countries and over 1.1 million people under continuous follow-up by DSS in 28 field sites. In Tanzania, there are DSS systems running in 6 rural and 2 urban Districts. Tanzania will be the first country where the idea of sentinel DSS sites in a national HMIS will be tested. The INDEPTH network has established a Malaria Task Group led by the DSS site at Manhica, Mozambique, to assist the 27 African DSS field sites working in malarious areas.

DSS Field Sites in Africa - 1998

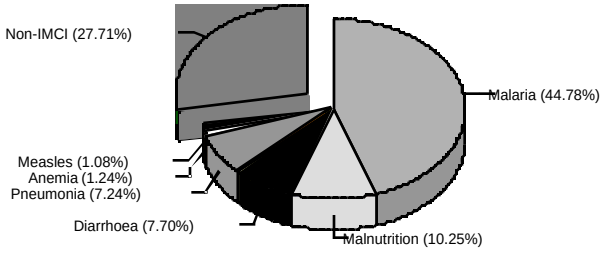


But can DSS be used to monitor the effectiveness of strategies to roll back malaria?

Roll Back Malaria is not advocating vertical, malaria only approaches. It is talking about broad system wide changes and integration. Integrated Management of Childhood Illnesses (IMCI) is a case in point. The effectiveness of IMCI will be determined by a myriad of operational and behavioural features including coverage, utilization, provider and user compliance, diagnostic accuracy, efficacy of the anti-malarial drugs, referral, etc. If IMCI is effective, we should see a reduction in proportional IMCI preventable mortality, even if other causes such as HIV are to increase. Within the IMCI causes, the non-specificity of verbal autopsy for malaria is no longer an issue. Because the DSS documents all mortality, we are able to see shares of the whole. To have plausibility in attributing a decline in IMCI preventable mortality to IMCI effectiveness, we need to document process indicators relevant to IMCI by linking the IMCI household and health facility surveys into sites where the DSS sentinels operate. An INDEPTH Collaboration of four DSS sites, two with IMCI and two without IMCI is piloting this approach now in Tanzania.

Under 5 Burden of Disease - Morogoro

YLLs Addressable by IMCI



Source: Tanzania Ministry of Health, AMMP and TEHIP Teams, 1998

Conclusions

In conclusion. To sum all this up, we have important deficiencies in HMIS and survey style information sources. If there is one take home message I want to emphasize, it is that sentinel surveillance of all cause mortality at the household level through DSS may be our best chance 1) to obtain the least biased picture of current, initial malaria burdens and critical utilization behaviours; 2) to influence national policy and resources for integrated malaria control; 3) to document trends in disease burdens over time; and 4) to monitor effectiveness of Roll Back Malaria strategies.

But this still leaves the question of who should take ownership of health information for RBM - whether it be a DSS approach, or conventional HMIS, DHS etc. Most national information systems necessarily operate to support a wide sectoral requirement. Most of the interventions proposed to RBM at the national level will not be "malaria-specific" - for example, management of anaemia in pregnancy; management of childhood illnesses; improved drug-supply and rational prescribing, etc. Information, whether on process indicators or impact assessment, will be cross-cutting and demand ownership by, and integration into the wider health sector. Where then does the responsibility for malaria information lie and how can this be supported to meet the needs of RBM? RBM will be a component of improvements in health service delivery generally and therefore this raises the issue of who should drive Health Information Systems for Roll Back Malaria at country level.

As a closing perspective on this. We must accept that we will never have all the time, resources and information that we would like. But we may be able to re-allocate some of our existing time and some of our current resources to generating community based information on the burden of mortality and on health seeking behaviours specifically associated with this burden. These are two of the most important statistics which we must influence and monitor. Since most of the disease burden in Africa is under-pinned by malaria, we must push for and explore such re-allocations. Re-allocation of some resources from comprehensive, facility based MIS, to a sentinel, community based DSS system may emerge as our most cost-effective option.

As long as malaria tops the burden of disease in Africa, we, as the malaria control community, must not shy away from a role as "pathfinder" to strengthen Health Information Systems in Africa.

HIS for Malaria: the example of the MARA/ARMA network

Marlies Craig, Medical Research Council, Durban, South Africa

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Uwe Deichman, Don de Savigny, Etienne Fondjo, Colleen Fraser, Eleanor Gouws, Imo Kleinschmidt, Pierre Lemardeley, Christian Lengeler, Dave le Sueur, Judy Omumbo, Bob Snow, Brian Sharp, Frank Tanser, Thomas Teuscher, Yéya Touré

It is an honour to be able to represent in this forum a network of scientists, who have made possible what most people deemed impossible, through their personal interest, dedication and contribution. MARA's achievements are the achievements of these individuals working together as a team towards a common goal. MARA is not an organization, it does not have a centre where things happen; it is a true network that is as strong as the people it consists of. MARA is a true partnership - not only between these individual scientists, but between different countries, different disciplines, different institutions, even of different funders.

You have now heard the Mapping Malaria Risk in Africa project being mentioned several times since Sunday evening, but Where does MARA come from? What does MARA do? Where is MARA now? Where is MARA going?

The origins of MARA

- The problem

We all know of the enormous problems malaria causes in Africa. We know of the renewed focus on malaria, and that many organizations are again dedicating their attention and resources to address the problem. We also know of the new tools that are available for controlling malaria today - such as insecticide treated nets, new drugs, improved formulations and packaging, rapid diagnostic tests, and still the hopes for an effective vaccine. But where to start? How to focus? What to do?

- The importance of information

Many factors influence the choice of how to control malaria in a particular region: malaria endemicity, vector species and behaviour, transmission seasonality, disease patterns, health services and more. Since none of these factors are distributed evenly across the continent, accurate, relevant and timely information on them is needed for malaria control to be planned and resources allocated properly. An increasing emphasis is being placed on evidence, so that the demand for an empirical approach to planning has grown.

- The value of maps

Maps offer an ideal way of displaying complex information in a way that is intuitively understandable and instructive. Everyone understands a map. They tell us not only what is happening, how much, but also where it is happening. A map is a powerful lobbying tool, which can be used to display to policy makers where the problem exists, where resources are employed, and possible discrepancies between the two. In South Africa for instance the spatial representation of malaria information has also led to more targeted malaria control, by pin pointing where malaria actually occurs, where control needs to be concentrated, and in fact, where control is not necessary.

The value of maps has been understood in the past, and malaria has been mapped in numerous countries, in some way or other. However, most efforts have been isolated and country-focussed, with malaria maps varying in their content, the way they were derived and their accuracy. While malaria and its control is increasingly being viewed as a continental rather than a national problem, a continental atlas of malaria, to analyse the big picture and target our efforts, does not exist.

- GIS in malaria control

Realizing the tremendous importance of space in the transmission of malaria, a geographical information system - or GIS - was started at the National Malaria Research Programme of the South African Medical Research Council in Durban in 1989 which focussed on mapping malaria risk in South Africa (1). Using GIS in health was a relatively new idea then, but it proved to be just the right thing to pinpoint exactly where the problem areas were and where to focus control efforts. The GIS group at the MRC developed considerable expertise in GIS and database management pertinent to malaria control, and this came to the attention of IDRC during a meeting on GIS for health and the environment held in Sri Lanka, 1994.

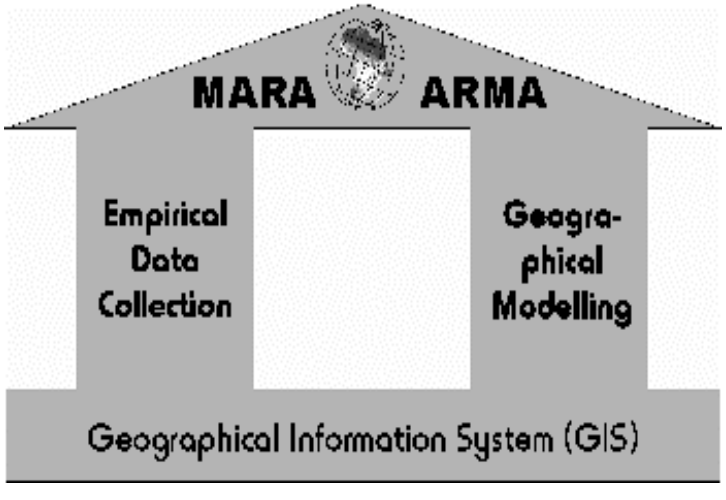
- The great plan

At the same time a need emerged to better understand the distribution of malaria transmission intensity, in the light of new control interventions and their short- and long-term effects (2). And as happens when great ideas come together and meet on common ground, the concept of MARA was born when Don de Savigny and Bob Snow proposed the development of a Pan-African collaborative network to map malaria risk, using the malaria GIS skills in South Africa as a platform. With support from the IDRC, Wellcome Trust and WHO/TDR, a series of workshops were held which developed the conceptual design of MARA (3).

What has MARA achieved?

From the start it was clear that MARA had to be built on two parallel and complementary approaches: a collection of existing empirical data and geographic modelling of malaria, both on a common GIS platform (Figure 1).

Figure 1. MARA Conceptual Framework



- Data collection

Large volumes of malaria surveys have been carried out by ministries, control programmes, research- and other organizations in the past. Unfortunately these data have been little used, poorly archived and risk being lost for future use. In the face of current needs for targeted and informed intervention, it is clear that all existing empirical data need to be brought together in one place, where they can be organized and accessed.

MARA started out with the bold intent of collating all possible published and unpublished data that could be located in sub-Saharan Africa. Since nobody knew what kind of format the data would be found in, a data collection system was designed that was flexible, but which at the same time standardized the collection process. Data are reported in a wide variety of different formats, but to be useful, have to be brought into one standard database. The proforma consists of separate sections that can be assembled as necessary, depending on the type and style of the reports (4).

- Database model

A relational database was then designed to accommodate the full complexity of all data relationships (Figure 2). The structure permits future growth, incorporation of new data entities, and a flexible means of combining data queries for analysis.

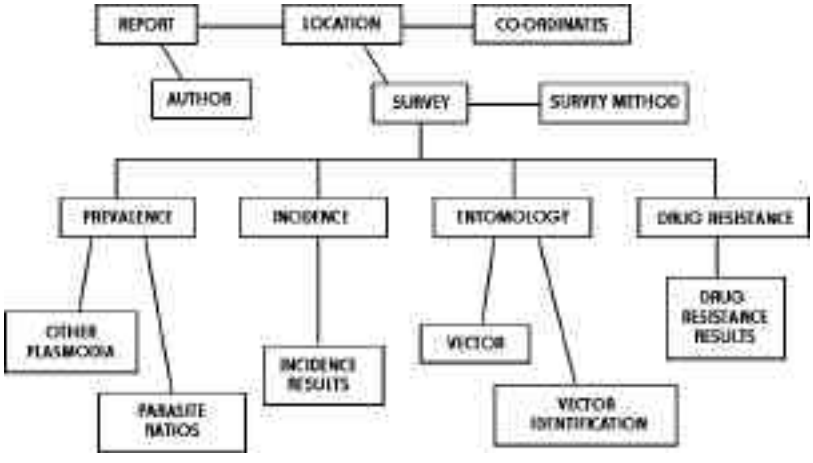
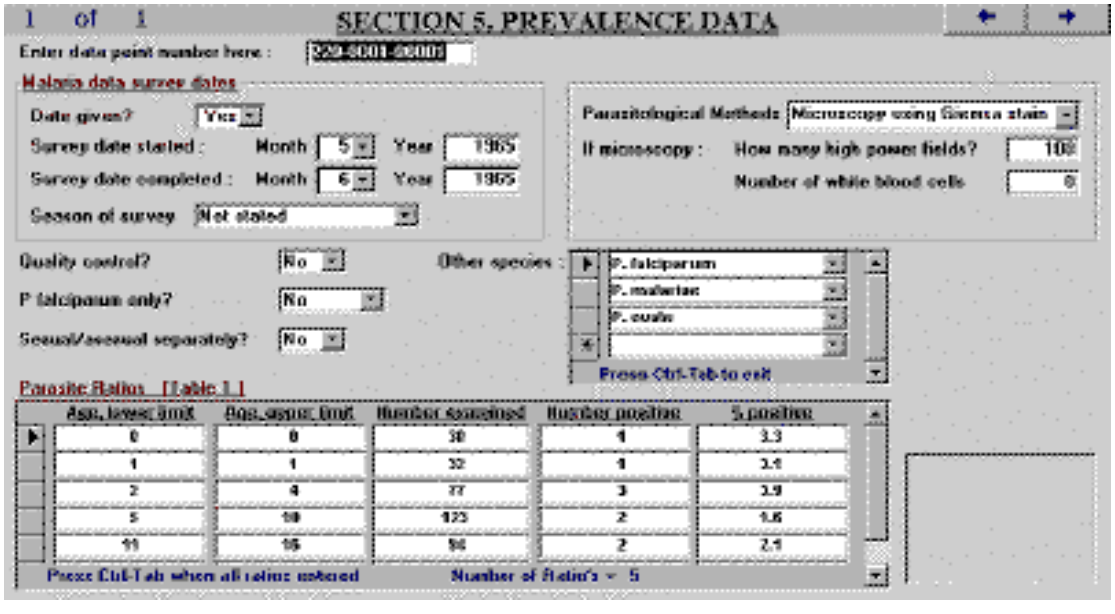


Figure 2. MARA database structure

- Data entry system

A stand-alone data entry software application, conforming exactly to the pro-forma, was created to make the data entry as easy as possible and to ensure standardisation (Figure 3).

Figure 3. Example of data entry screen



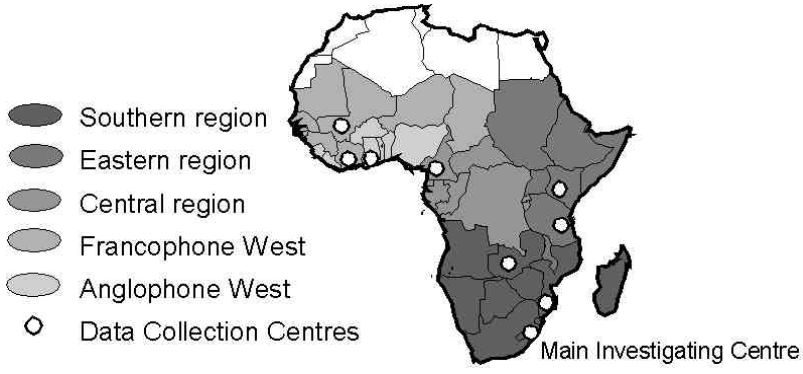
- Geo-referencing

Finally, to be able to integrate the data in a GIS, all surveys had to be "geo-referenced" (i.e their latitude and longitude determined). If the exact location of the survey site was not given in the report, it was obtained by searching for the place names on a topographical map, or by using digital maps and databases.

- Data collection regions and centres

For the data collection process Africa was divided into functional regions, with five regional centres and two sub-centres responsible for 5-7 countries in their region (Figure 4). The regional centres are located at existing institutions throughout the continent, each with a co-ordinator and a co-investigator, which make up the main MARA team. These people are established scientists who contribute part of their time to MARA activities.

Figure 4. MARA regions and centres



Many different strategies were applied to search for the data, including Medline and Embase searches of published literature, hand searches of relevant journals, and cross-referencing bibliographies. Further data was obtained by contacting researchers and authors known to have worked in a particular region. The data coordinators then began visiting all identified institutions likely to hold unpublished documents in the countries of their region. This included relevant ministries, universities and research institutions. Finally, international archives in Africa and Europe (WHO Geneva, Paris, Antwerpen, Lissabon) are being searched and all identified documents abstracted (5).

Figure 5. Data points collected by the end of 1998

- Data points collected to date

It is clear that such an ambitious task takes at least several years to complete, but if we look at the data that has been collected so far, it is remarkable how much has already been found. You can see that some countries are well covered, whereas others are sparse in data, still need to be visited or are presently inaccessible.

- Geographical modelling

This brings us to the second focus of MARAgeographical modelling. What is it and why do we need it? Prevalence data on their own are

not enough to give us the whole picture of the status of malaria. Also, they do not cover the entire continent - as we saw, there are large data gaps, many of which will not be filled because data don't exist there. modelling does is to fill the gaps and to answer some of the major questions that interest us.

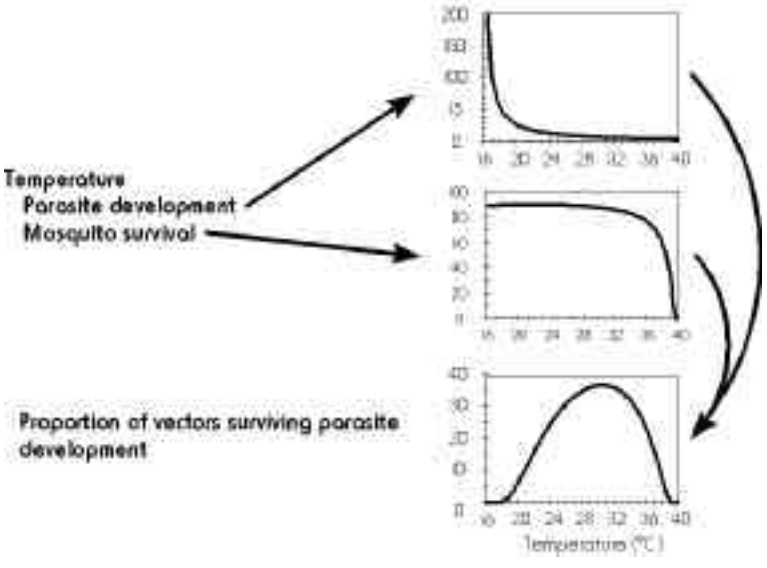
- Modelling: questions and scales

What are some of these questions? The kind of questions we are interested in is where does malaria exist (distribution), how intense is the transmission (endemicity), when and for how long is malaria transmitted (seasonality) and what are the factors that cause these differences? These questions can then be addressed at different scales: we can look at the large, continental picture, we can focus on large regions with imilar ecologies or climates, or we can focus on the country or a group of neighbouring countries.

Figure 6. The effect of temperature on parasite development

-The main limiting factors of malaria

Malaria is an environmental disease that is strongly affected by the environment. There are numerous factors that determine the particular malaria situation from one place to the next. However, the two major factors that limit the distribution of malaria are temperature and rainfall. Rainfall is the source for mosquito breeding sites and determines humidity, which affects vector survival. Temperature affects many parts of the transmission cycle, but its effect on the development of the parasite in the vector, and on vector survival are the most pronounced (Figure 6).



The proportion of mosquitoes surviving the parasite's sexual development is the major component in determining whether or not transmission takes place (6).

- Malaria distribution and seasonality

At the continental level, two models have been developed. The first (7) defines the distribution of endemic malaria, based on the biological constraints placed on the parasite and the vector by temperature and rainfall, as outlined before. The particular temperature-rainfall combination is rated as either suitable or unsuitable for transmission in the average year (Figure 7). I say "in the average year" because the climate data we used are long-term climate data which give the average conditions over the previous 60 years.

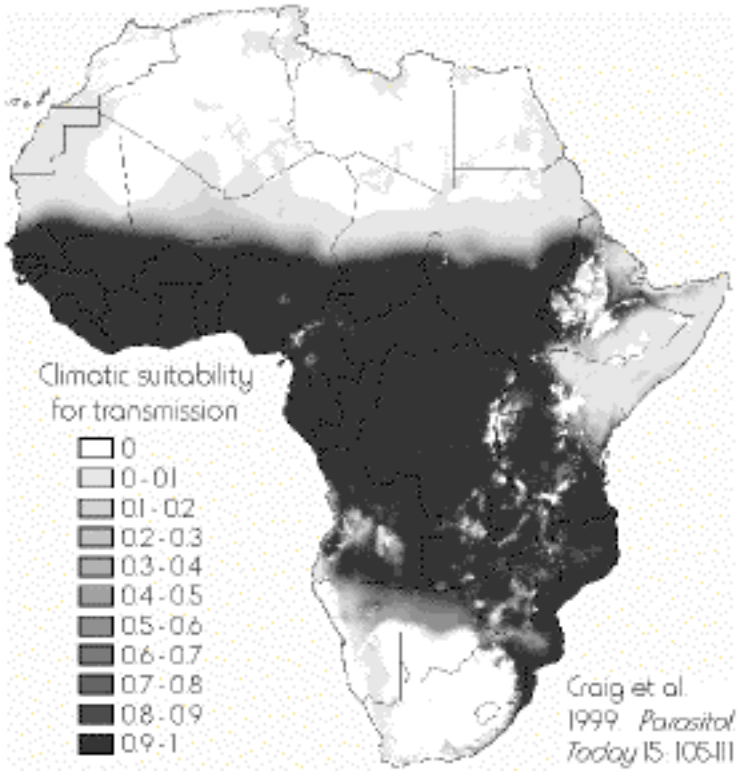


Figure 7. Malaria distribution model

The model agrees well with what maps we have on malaria distribution, its benefit being that it was derived in the same way all over the continent, and that this process can be repeated, refined and tested.

The continental distribution model was the first product to come out of MARA and put us into a position to take a look at malaria in African highlands, within the HIMAL project. Because it is a numerical model, it can be mathematically combined with other models, such as a population distribution model, which allowed us to estimate the continental morbidity and mortality of malaria in a repeatable and empirical way (8). The work on the continental burden of disease will be discussed in more detail by Dr Nabarro.

The second continental model defines the duration of transmission in months, at the same time indicating the first and last month of the transmission season (9) (Figure 8). This information is obviously important to the choice and timing of interventions such as spraying of residual insecticides. Different interventions may be suited better under different situations of malaria seasonality.

Figure 8. Malaria seasonality model

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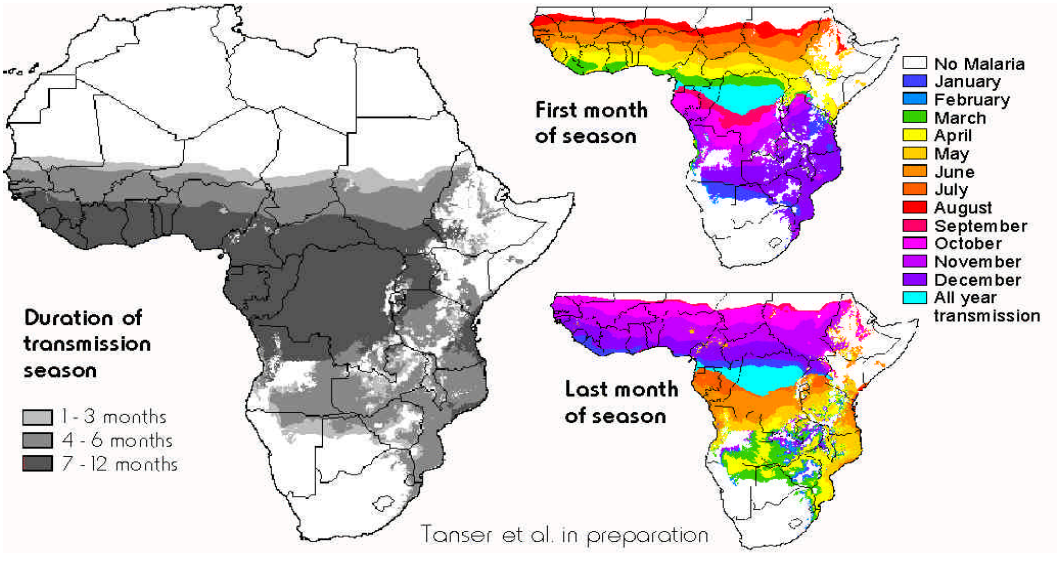
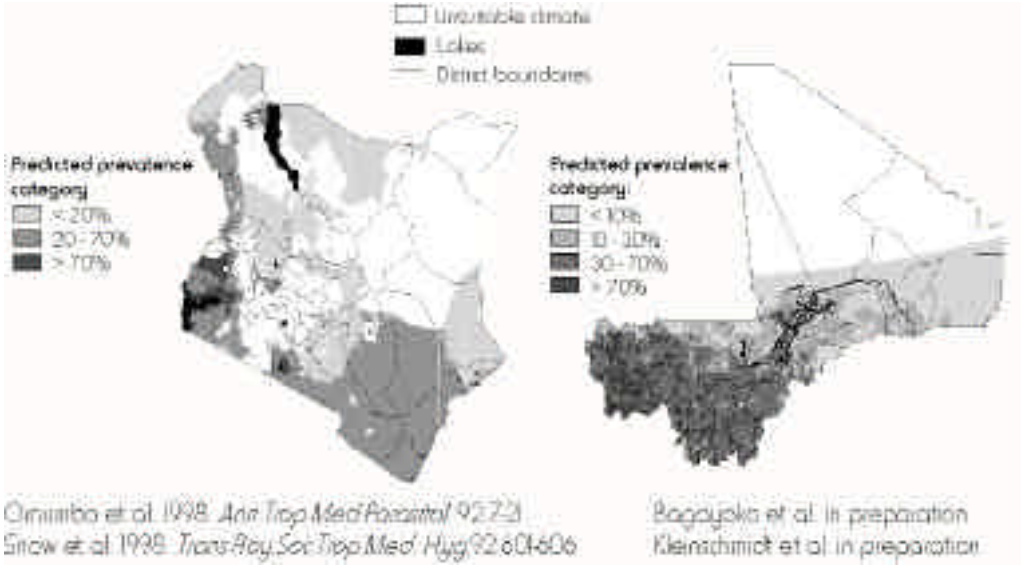


Kenya and Mali models

The regional centres have started using the empirical data at the country level to derive malaria endemicity models by statistical analysis against determining factors such as climate and the presence of water bodies (Figure 9).

Figure 9. Statistical malaria endemicity model.



Magaran Bagayoko presented the work done in this regard in Mali (10), and Judy Omumbo will give you more detail later on what has been done in Kenya (11).

Where is MARA now?

As you have seen, much data has already come in, but much still needs to be collected. Some models have been done, but they still need refining, and other models need to be developed. With the funding awarded recently by MIM, MARA has been able to continue its work.

As mentioned, the modelling of malaria endemicity, based on the empirical data, which is a major aim of MARA, has begun in two countries. The Kenya and Mali centres have broken the ground, so to speak. We are dealing with a new approach to health statistics, and several statisticians are working on the problem how to handle such unlikely, and in some ways, non-ideal data. New statistical methods may have to be developed and many methodological problems still need to be solved before we can seriously approach the rest of the continent in terms of defining endemicity.

MARA has been operating on minimal funds, and this has clearly hampered our ability to distribute initial products that have come out of the collaboration so far. Fortunately Roll Back Malaria is now sponsoring poster-map production, which will start in full swing in April, and through which all endemic countries will be supplied with poster-sized maps of those products available so far.

Where is MARA going?

Obviously, we are working towards our ultimate goal of providing an atlas of malaria risk in Africa, both as a book and in digital format, which will allow for future updating. We aim towards public access of collected malaria data and maps, in the form of posters as well as

via the Internet. Along this road towards an atlas, we have published the first technical report, which you have all received, which covers the work done to date and we would appreciate your comments and opinions by filling in the questionnaire included.

MARA has come a long way since its beginnings. The regional data collection centres are slowly being joined by country centres, where individuals buy into the aims and goals of MARA and take on the MARA related activities and data collection within their own countries. This is a great development, since finding hidden data sources in your own country is always easier than in someone else's. But more than that, this increasing involvement of dedicated individuals at country level is strengthening the network, building up local GIS capacity and increases the long-term survival chances of MARA, which is important if the repository of data is to be kept up-to-date.

Another important development is that as MARA is gaining more momentum, the web of contacts and partnerships continues to grow. As a result of this, different interest groups are starting to crystallize, focussing on more specific aspects that have emerged over time. So there are groups focussing specifically on modelling and statistics, vector distribution and entomological data, drug and insecticide resistance, the use of satellite imagery, and so on.

The data collected and the work being done by MARA has incredible potential to support control activities in countries, and Judy Omumbo will now give you some insight by giving you the example of work done as part of the MARA project in Kenya.

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The MARA/ARMA Collaboration and Health Information Systems for Malaria Control: An example from Kenya

Judy Omumbo, Kenya Medical Research Institute/Wellcome Trust Collaborative Programme Programme, Nairobi, Kenya

Summary

Good information systems are vital to the success of malaria control programmes in Africa. Although different groups involved in malaria control in Kenya routinely collect many data on malaria there are gaps in information transfer between the research and the malaria control communities. One way of bridging this gap is to facilitate inputs by both parties at each stage of the information development process and to provide research results in a format that is clear and relevant. This paper presents the beginnings of the development of a Geographic Information System based Malaria Information System initiated and developed by malaria researchers and the National Malaria Control Programme in Kenya.

Background

Compared with other diseases, relatively little empirical information is readily available to malaria control workers in Africa for defining and evaluating the impact of disease. Studies of malaria in 5 areas of differing epidemiology across Africa show that the clinical spectrum and age profile of severe disease are related to intensity of transmission[1]. The effectiveness of different control interventions is likely to be related to the level of endemicity[2, 3]. A geographical description of endemicity such as is provided by a map is therefore an essential tool for both epidemiologists and control planners to use as a basis for decision making on appropriate interventions and resource allocation.

Malaria researchers in Africa have recognised the need for a comprehensive malaria atlas and the MARA / ARMA Mapping Malaria Risk in Africa (MARA) international collaboration was set up in 1996 with a view to addressing this need[4]. The past decade has seen accelerated developments in the field of Geographic Information Systems (GIS) which involve computerised desktop mapping and relational databases. This paper looks at the ways in which MARA has used GIS to develop tools for malaria information management in Kenya. A key objective of MARA is to make data available to national malaria control teams in order to promote information-driven approaches to malaria control. To this end, MARA has operated in Kenya at three levels. The first has been the development of a malaria risk stratification model. Secondly, this model has been used to identify populations at risk of different epidemiological scenarios of malaria and thirdly the information has been fed into the National Malaria Control programme where one of the results has been the setting up of a Malaria Information System.

Materials and methods

i. Empirical data sources:

Since 1996 a comprehensive search for all published and non-published malaria prevalence data from cross-sectional surveys of children less than 10 years old has been conducted in Kenya[5]. Searches of journals, Ministry of Health records, books, postgraduate theses and research reports identified over 800 studies dating from 1929 to 1997.

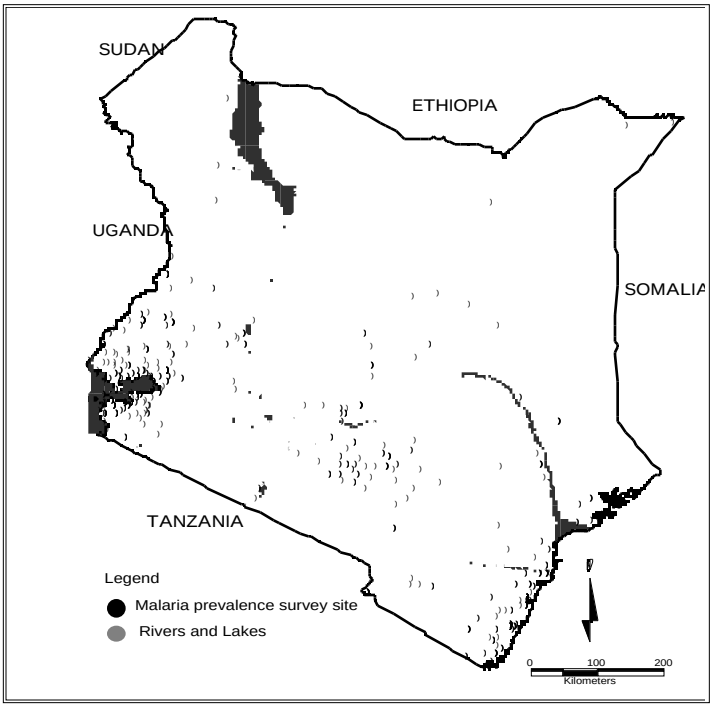


Figure 1: Locations with cross-sectional parasite ratio data[5].

Each survey was geographically referenced and mapped using the GIS software MapInfo[6] (Figure 1). Since the parasite ratio (PR) data collected are derived from surveys conducted over a long period of time, an assessment of the stability of this endemicity marker over time and across different age groups was conducted. This assessment showed that the measure remained relatively stable over time, place and age classes within the broad definitions of high, moderate and low transmission intensity.

ii. Classification of endemicity:

The development of both the malaria parasite and the vector are dependent on ambient temperature and thus climate drives the distribution of transmission[7]. This was used to define the limits of unstable and stable transmission and also the intensity of transmission within stable endemic areas. There are two settings in which unstable transmission occurs in Kenya; in North Eastern Province where transmission is limited by low rainfall and in the highlands west of the Rift Valley where low temperatures limit transmission. Stable transmission areas have been stratified using both climate and parasite ratio data from community based parasite prevalence surveys conducted in Kenya since1960. Areas of high stable risk have been defined as those where the PRs in childhood are Δ 70%, low stable transmission areas are where PRs are less than 20% and moderate transmission areas have PRs of between 20 and 69%. 124 community based parasite ratio surveys of children aged 0-10 years were selected from the larger data set for use in the model. Linear discriminant analysis was then used to stratify geographical areas of stable malaria endemicity according to low, moderate or high levels of risk based upon climatic suitability for transmission. The model was able to correctly classify 75% of the empirical PR data[8].

Results

i. A model of malaria endemicity:

The resulting transmission intensity map shows that Kenya experiences the whole range of malaria epidemiological conditions across the country[8] (Figure 2). Highest transmission intensities are experienced along the Indian Ocean coastline at Kwale in the south east of the country and around Lake Victoria in western Kenya while large areas of the country lie within unstable or low, stable endemic conditions.

ii. Stratification of populations at risk

The next step involved apply the risk map to population distribution to determine who is at risk from what level of malaria[9]. Population data for each sublocation were obtained from the 1989 national Population Census and projected to 1997[10]. Using the GIS , the total number of persons per fourth level administrative unit (location) living within each stratum of endemicity was determined (Figure 3).

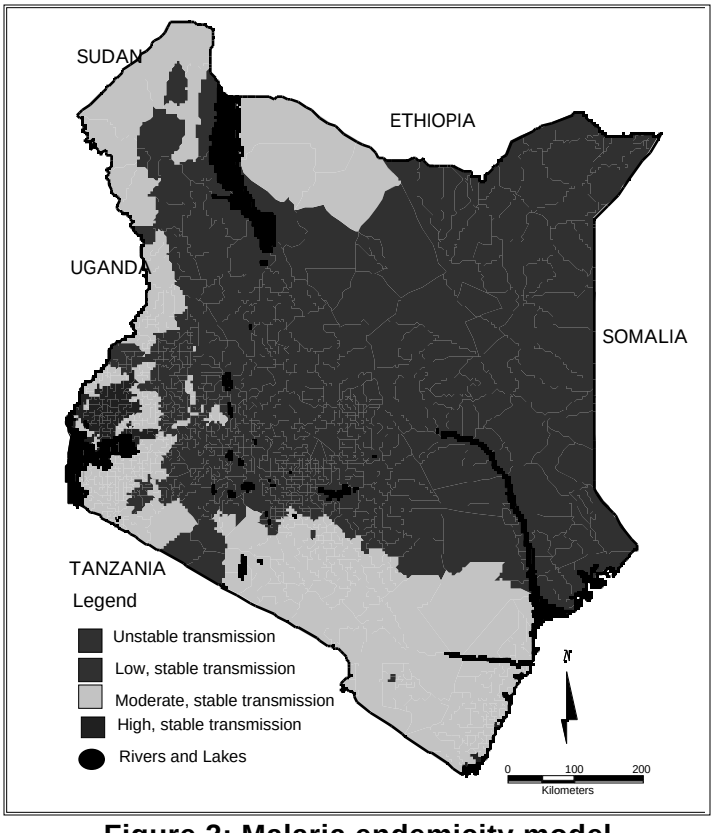
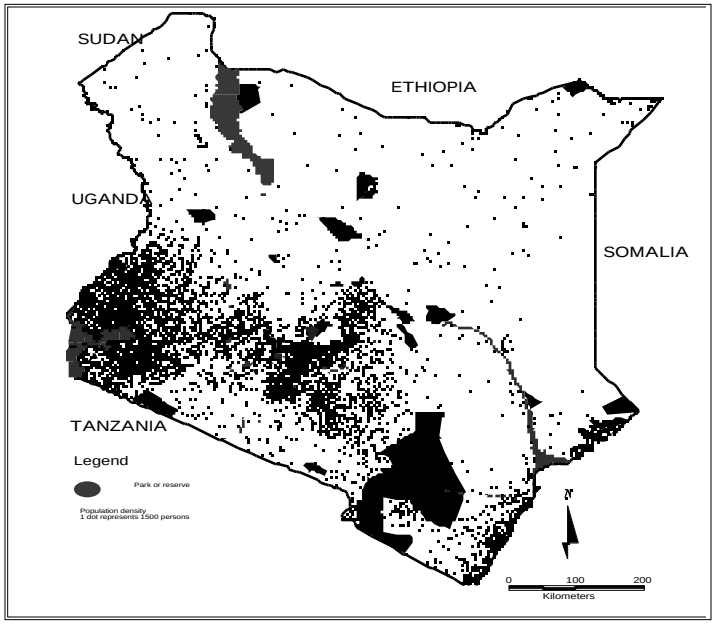


Figure 2: Malaria endemicity model.

Figure 3: Population distribution (1989 national census estimates projected to 1997)



Roughly half of Kenya's population live in areas of moderate to high stable malaria transmission whilst the remainder live under conditions of either low parasite exposure or unstable conditions (Table 1).

Malaria endemicity classification	Percentage
High Stable	**13**
Moderate stable	**40**
Low Stable	**17**
Unstable	**30**
Total	**100**

Table 1: Distribution of populations at risk by malaria endemicity classification.

iii. Estimation of malaria mortality risk:

Malaria mortality rates have been estimated under different scenarios of endemicity in Africa[9]. These rates have been applied to population groups to produce estimates of malaria's disease burden as it affects Kenya (Table 2). Approximately 26,000 children under the age of 5 years die of malaria yearly. This translates to 72 childhood malaria deaths in the country each day. Within rainfall limiting unstable areas, malaria mortality is estimated as zero but this may rise to between 3,000 and 14,000 deaths during an epidemic. Estimates for disease burden during pregnancy are only available for moderate to high stable endemic areas. Based upon these data, approximately 6000 women living in these areas will suffer an episode of severe malaria anaemia each year.

	Temperature limiting unstable malaria and low stable endemicity	Moderate stable endemicity	High stable endemicity
Numbers of deaths among 0-4 year olds per annum	**1,223**	**18,293**	**6,614**
Numbers of severe anaemia events among Primigravidae per annum	**N/A**	**4,311**	**1,567**

Table 2: Estimates of malaria mortality by risk group and endemicity class[9].

iv. Links with the National Malaria Control Programme:

A key aspect of the success of malaria control is the establishment of links between research groups and control specialists. Collaboration has been established with the National Malaria Control Programme and through this we shall be able to further define populations at risk, to look at drug requirements and the spread of resistance, and to rationalise control activities in the country. By way of example the distribution of Insecticide Treated Bed Net (ITBN) activities in the country has been examined[11]. A questionnaire-based study was conducted to quantify the groups and populations involved in Community Based Health Care (CBHC) activities and those that carry out ITBN related activities identified. Each Non-governmental organisation, research group, mission, Ministry of Health or other health provider was asked to list the areas where their activities are targeted. The sites were then mapped using GIS. The resultant map shows how bed net programmes are concentrated in areas of low risk, which are also sparsely populated as opposed to the densely populated high and moderate transmission areas of Western and Coastal Kenya (Figure 5).

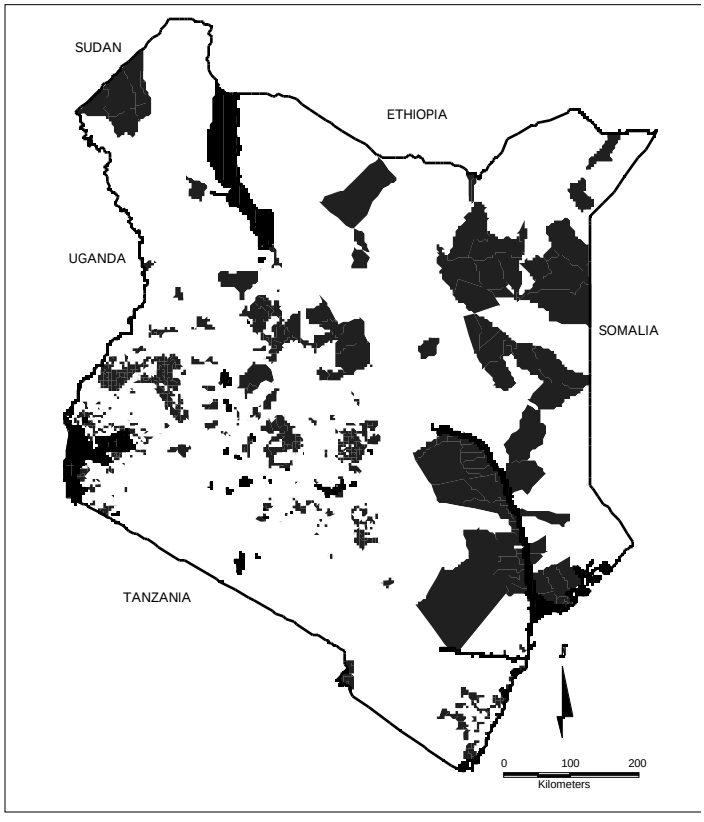


Figure 4: Target populations for Insecticide Treated Bed Nets or intervention study sites (gray)

Good information systems are vital for the success of healthcare programmes and it is hoped that these beginnings will provide a platform for more information-driven control programmes in Kenya in the future.

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BREAKOUT SESSIONS: HEALTH INFORMATION SERVICES

Programme

1. Data Needs for Malaria Control I.

Chair: Dr. Christian Lengeler

Rapporteur: Ms Marlies Craig

Presentations (15 minutes each)

1. National Health Statistics – quality and use - Penny Philips-Howard
2. Linking demographic surveillance to health service needs – The TEHIP/AMMP experience in Tanzania - Don de Savigny
3. Computer assisted health information systems for malaria control - Brian Sharp
4. GIS for malaria mapping in Mali. - Magaran Bagayoko

   Discussion (45 minutes)

2. Data Needs for Malaria Control II.

Chair: Dr. Don de Savigny

Rapporteurs: Dr. Pierre Ngom, Dr. Penny Philips-Howard

Presentations (15 minutes each)

1. Population surveillance to measure mortality – the INDEPTH network - Ricardo Thompson
2. The potential role of government mortality statistics in the evaluation of the efficacy of ITBN - John Arudo.
3. Health service surrogate markers for monitoring drug resistance and the EANMAT network - Theonest K. Mutabingwa
4. Measuring quality of clinical care – the IMCI experience - Doyin Oluwole

   Discussion (60 minutes)

3. Epidemic Preparedness and Data Needs.

Chair: Dr. Charles Delacollette

Rapporteurs: Dr. Charles Ravaonjonahary, Mr. Steve Connor

Presentations (15 minutes each)

1. The highland malaria project - Jon Cox
2. Climate and malaria forecasting - Mark Jury and Macol Stewart
3. Preparing for malaria epidemics in Namibia - Richard Kamwi
4. Highland malaria in Uganda: Epidemic transmission at low vector densities - Kim Lindblade.
5. Control of epidemic malaria on the highlands of Madagascar - Franco de Giorgi.
6. The relationship of malaria outbreaks to preceding meteorological conditions in Zimbabwe - Washington Zhakata

   Discussion 30 minutes

Summary Report: Health Information Services

Introduction

Through the brokering of new partnerships at the international and national levels, RBM has created a new era for malaria control in Africa. To retain credibility within the eyes of the donor community and the population of Africa who continue to suffer from the growing adverse consequences of malaria infection, precise information is required on the current distribution and magnitude of the disease burden; demonstration of appropriate allocation of wider health sector funds in accordance with the burden; and ultimately that the optimistic hopes that reducing the burden by 50% by the year 2010 has been attained.

Reliable health Information provides the power to define needs, identify problems, effect change and monitor impact. Information necessary for malaria control operates at various levels:

- Credible information on the burden of malaria and its impact upon the social, economic and demographic structure of country. Such "advocacy" information is paramount to solicit appropriate action by national governments and international donor commitment.

- District-level information on disease burdens, clinical and seasonal patterns and spatial distribution allow appropriate and targeted allocation of limited resources within financially constrained environments to achieve maximum return on investment in health.

- Information on use and quality of allocated services for malaria control and prevention by target populations allow programmes to be constantly monitored, feeding back into revised action and financial plans.

- The measurement of the health-impact of targeted malaria services provides district, national, regional and international health professionals in definition of their return on investment.

Summary of Presentations

- New and old approaches to measuring disease burdens and risks [1]:

There exists a wide and varied source of health information systems that operate within the African region which could be used within the context of malaria control. Demonstrations that traditional Health & Management Information Systems (HMIS) provide inequitable distribution of district-level health resources in Tanzania highlighted the need to revisit their future value for RBM within the framework of health sector reform (De Savigny). Regional differences may exist in the completeness and coverage of information obtained from national HMIS or civil registration systems. In Western Kenya seasonal patterns of mortality were consistent between detailed population surveillance estimates and those derived from the local registrar of births and deaths (Arudo), HMIS data may be a valuable resource for local management of resources, definitions of local malaria epidemiological patterns (Philips Howard) and monitoring secular trends in disease for surrogate markers of drug resistance (Mutabingwa) or epidemic predictions under conditions of unstable

[1] See also plenary presentation by Don de Savigny

malaria (Lindblade, Zhakata, Kamwi). Specialised uses of HMIS data may provide reliable markers of seasonal disease patterns and relative impacts of targeted community-based interventions (e.g. ITBN) (PhilipsHoward). However there was a clear demonstration that the precise nature of the malaria burden at the household level was not captured through facility-based surveillance systems.

To obtain reliable estimates of disease burden at the household-level demands intensive, longitudinal household demographic surveillance (DSS). Such systems have, in recent years, been established in three districts of Tanzania and their output has been used to redistribute health resources by District Health Management Teams (DeSavigny). DSS sites in Africa were first established in Senegal during the 1960's. During the mid-to-late 1980's there has been a proliferation of DSS sites created by epidemiologists and demographers to understand the epidemiological basis of mortality and to test the impact on mortality of new interventions through individually or community-randomised controlled trials. DSS sites are characterized by household censuses, monitoring of vital events (births, deaths and migrations) and examinations of causal factors of mortality and the circumstances (including treatment-seeking behaviors) surrounding each event. Whilst infant and childhood mortality remains unacceptably high in much of sub-Saharan Africa deaths are comparatively rare events and DSS surveys require large populations. In response to the diverse nature of the casual structure and epidemiological basis of mortality in Africa and the need to pool resources and information, a network has been created to link DSS sites across Africa - INDEPTH (Thompson). This network currently involves 23 sites in Africa with approximately 1 million people under surveillance. It is envisaged that this network will provide a powerful resource for monitoring the long-term impact of initiatives created through the RBM movement and that the numbers of sites and population under surveillance will continue to grow (Thompson).

- Monitoring & evaluation

Monitoring and evaluation is critical for guiding disease control programmes. Several examples of M&E were provided during the presentations including those developed to support IMCI (Oluwole) and a regional network to monitor drug resistance in East Africa, known as EANMAT (Mutabingwa). These specialised surveys provide additional "process" and impact information not achieved through routine health statistics or demographic surveillance. Monitoring the quality of clinical care and the efficacy of anti-malarial drugs enables programme managers to re-orientate existing strategies to meet newly defined weaknesses and needs.

- New technologies [2]

Information technology and globally available data sources have provided new opportunities for health information specialists and epidemiologists working in malaria research and control. In South Africa the close collaboration between the research and control communities has enabled the transfer of new technology to improve the quality, processing speed and use of malaria information through the establishment of a computerized system of direct case-data entry at the peripheral levels of the health service (Sharp). This system has engendered increased value in the information generated by those who record the data. Mapping malaria risk has a long tradition in Africa, however, the advent of new computer tools, Geographic Information Systems, have provided a more powerful means of capturing, storing and displaying spatial malaria information. In Mali,

[2] See also plenary by Marlies Craig and Judy Omumbo

these new tools have been combined with statistical approaches to define high resolution endemicity risk maps providing malaria control programme managers with a visual image of the country's high, moderate and low intensity transmission risk areas (Bagayoko).

- Epidemic preparedness and data needs

Whilst unstable transmission areas constitute a low morbid and fatal risk to the population on an average year, these areas are characterised by large scale inter-annual variations in risk leading to high disease burdens amongst the entire population. Unstable areas of malaria transmission in Africa present a special need for monitoring systems including the geographic location of these at-risk communities, monitoring changes in disease risk and the predictive value of the climatic determinants of inter-annual variations in disease risk.

The Highland Malaria Project (HIMAL), a component part of the MARA Mapping Malaria Risk in Africa initiative, has initiated a detailed search and analysis of the African literature related to malaria epidemics. These data were combined with climatic and topographical data within a GIS platform to provide new insights into the limits of epidemic prone areas of East Africa (Cox). HIMAL's new research agenda will focus on further detailed analysis of other risk factors (including land use, drug resistance and population movements) through prospective studies across the international borders of Tanzania, Uganda and Kenya.

Forecasting epidemics has always been difficult, not least because long-term data series are often not available. A model has been investigated using the relationships between rainfall and temperature proxies and epidemiological records from eastern South Africa over a 35-year period (Jury & Stewart). The system allows for a lead-time of 5-6 months and has been operational for the past 4 seasons with a 'success rate' of 75%. The constraints and use of available epidemiological surveillance tools were also provided by control programme managers from Namibia (Kamwi) and Madagascar (Ranavio), highlighting the practical applications of disease and climate monitoring in these areas of Africa. In a highland community of Uganda, East Africa, detailed epidemiological investigations were undertaken during at epidemic experienced at the beginning of 1998 demonstrating the health consequences of low intensity transmission upon all age groups (Lindblade). Whilst climate drives the likelihood of epidemic risk in Southern Africa (Jury & Stewart; Kamwi; Zhakata) in East Africa the risks of epidemics may involve more complex and wider series of parameters (Cox, Lindblade).

Breakout discussions

The participants from the control community articulated the issues associated with maintaining HMIA in their respective countries (Rwanda, Namibia, Zambia, Botswana, Zimbabwe and Ghana).

There was a much greater familiarity with HMIS than DSS by control programme staff. In addition there was a comparative difference in the apparent use of HMIS data between Southern Africa and the rest of sub-Saharan Africa, among the former countries there was a perceived value in the HMIS system for monitoring malaria control programmes. Nevertheless a consensus view was expressed over the innate problems associated with HMIS including motivation of staff, understanding of why data was being collected, unwieldy and multiple data forms, poor feedback, lack of appropriate training in data analysis and uncertainty in completeness of information. The latter was perceived as

particular problem in areas where poly-pharmacy was a common leading to many disease events would being missed at the formal health service point.

The precise translation of information into action and decision making was well articulated for IMCI (Oluwole) and resource allocation in Tanzania (De Savigny) but concerns were raised on how information generated at health facilities and through GIS could actually be used by health planners.

The costs of DSS were discussed in the light of those under surveillance versus the use of sentinel DSS to provide nationally representative estimates of disease burden where the latter represents only 0.03 US$ per capita. It was suggested that indirect demographic techniques, such as the preceding birth technique and Brass's Children-Ever-Born method, be tested against direct demographic surveillance with a view to reducing costs. No one had any comparable costs for HMIS in Africa however it was highlighted that sentinel approaches to HMIS disease surveillance were currently being developed by WHO in Africa.

Overall it was clear but information needs to be tailored in accordance with epidemiological and demographic circumstances. Urban and rural differences in health service utilization may lead to biases in routine HMIS data and active case-detection of infection rather than passive detection of disease should reflect the stability of transmission and immune status of the population.

In summary, the development of information systems should start with the definition of objectives, what type of interventions are required, and then define indicators, and which methods are most appropriate to capture the relevant data. Participants stressed the relevance of assessing the utilization of HMIS - since discussions seemed to polarize between DSS where high quality data which could be generated currently only in a few places, against the generation of masses of data through HMIS which is mostly of low quality. The importance of data collection methods which reach the homes was stressed since a high proportion of child mortality and morbidity occurs within the community. Finally the participants agreed on the importance of avoiding data overload, so that a critical minimum dataset was essential and that research was essential to define the most sensitive indicators.

Possible research agenda to address needs for health information to support malaria control in Africa.

Facilitators worked with the commentary provided by the control community during the breakout discussions to formulate a series of possible research questions to provide operationally relevant answers to better guide information systems for malaria control. This tentative agenda was then presented to the group for discussion, refinement and addition. The resultant list was as follows:

1. **Formative research** on the value and utilization of existing HMIS, National Demographic & Health Survey (DHS) and civil registration data at all levels of the health sector- who uses the data, for what, how long dose it take to collect, collate and forward, extent of district or national level feedback to data collectors, what is the value of the data (including tangible demonstrations of the use of the data for planning or managing malaria or disease control or prevention) etc.

2. **Qualitative comparisons** between traditional civil registration, HMIS, DHS (involving indirect demographic techniques) and DSS systems to establish coverage, accuracy and characteristics of missed mortality events.
3. Analysis of the **comparative costs** per capita of various surveillance systems aimed at measuring community-based mortality allowing for sensitivity and specificity of coverage.
4. Development of **new tools** for capturing information relevant to characteristics of district-level malaria control and prevention plans of action. The characteristics of these tools to depend upon the ecological and epidemiological characteristics of districts (e.g. epidemic versus stable transmission). Possible areas to explore would be the use of services during terminal disease events, quality of clinical care through exit interviews, use of blood transfusions as a surrogate marker of anti-malarial drug resistance, etc.
5. Development of **new analytical tools** which will assist planners at national, district, local levels to interpret and act on relevant health data.
6. Studies to examine ways in which HMIS can define health impacts of programmes aimed at malaria prevention.
7. For epidemic preparedness it was suggested that the outcomes should be a guideline on forecasting, early detection and control of malaria epidemic in Africa. To achieve this research is needed in the following areas:
   a. Which indicators to use in early detection.
   b. Forecasting tools producing simple summary indicators for use at district level. These should be developed outside the health sector by climate meteorological forecasters/food security and drought monitoring systems and made available to public health services.
   c. The development inter-country / country preparedness plans of action including forecasting / early detection instruments and adequate ready to use at any time control options where these do not exist.

Links between research and control

The group recognized that discussions were of a generic nature and not specific to malaria. This is particularly significant when developing partnerships between research and control communities. In the case of HIS a wide series of stakeholders must be consulted because research to practice will depend upon ownership by the entire health sector. For the purposes of demographic, epidemiological and health service surveillance malaria researchers and malaria control specialists must consult a much wider research and health service community. In several Southern African countries such intersectorial collaboration may be less relevant given that information systems for malaria control are run specifically by the malaria control programmes.

In order to insert and validate sometimes quite sophisticated new tools in the field of epidemic forecasting, it will be beneficial to improve collaboration between meteorologists and district medical officers / malariologists in selected provinces/districts prone for malaria epidemic. Furthermore, countries which have sophisticated and developed epidemic preparedness plans and forecasting tools should be assisted in facilitating such activities in and technologies in other regional countries with similar problems.

Capacity building

The donor community need to recognize the significance of DSS sites in Africa for the basic epidemiological understanding of the true impact of new interventions being developed within the framework of RBM. Such interventions include the role of home-based management of disease, combination therapy to reduce the evolution of drug resistance, the management of malaria in pregnancy, understanding mechanisms of natural immunity for vaccine development, determinants of epidemics to guide control and interactions between infectious and nutritional diseases and their management through IMCI to name a few. Perhaps the best examples of the power of long-term commitments of DSS are those provided by Trape and colleagues on the impact of emerging chloroquine resistance on mortality. Whether DSS will provide the best alternative to existing national HMIS systems demands further investigation, however, the value of DSS as research tools to support wider RBM decision-making is already clear. Investment is therefore required to build the continents capacity to maintain large-scale demographic surveillance systems. These commitments must have a long-term perspective - as with RBM's time-frame - changes in the health sector, new tools, drug resistance and their translation into changes in survival require 10-20 year investments.

MALARIA VACCINES AND IMMUNOLOGY

Plenary Presentations

Malaria Vaccine Status in Africa : Past Experiences, Lessons Learnt and future Perspectives.

Wen Kilama

Basic Research on Malaria Vaccines.

Steve Hoffman

Correlates of Immune : Practical Implications

Christian Roussilhon

What can we learn from Molecular Epidemiology?

Odile Puijalon

Breakout Sessions

Programme

1. Malaria Vaccines : Basic Research
2. Malaria Vaccines and Immunology
3. Malaria Vaccine Field Trials and Capacity Building

Summary Report

PLENARY PRESENTATIONS

Malaria Vaccine Status in Africa : Past Experiences, Lessons Learnt and Future Perspectives

W. L. Kilama, Chairman, AMVTN Coordinating Committee, Dar es Salaam,Tanzania

Introduction

Throughout this Conference it has been made abundantly clear that malaria, especially that due to *Plasmodium falciparum,* is Sub-Saharan Africa's bane. It is in this region where malaria is so devastating, causing more than one million deaths each year, and constituting an unbearable burden on the already overstretched health services. Country-specific statistics from tropical Africa almost invariably show malaria as the first or second cause of outpatient attendances, admissions and deaths in health institutions. To add to the misery, the African malaria situation is deteriorating fast. In terms of Disability Adjusted Life Years (DALYs), malaria ranks joint first with respiratory infections, accounting for 10.8 per cent of DALYs in the region. Yet experience from intervention trials in Africa show these figures to be gross underestimates. Economic appraisal would blame a good proportion of Africa's wretchedness on malaria; its direct and indirect costs are put at a staggering US$ 2,000,000,000 annually!

Malaria control in Sub-Saharan Africa is problematic to say the least. Vector control, which ousted malaria from much of Europe and North America, is for the most part impractical in Africa, except for the recently introduced insecticide treated materials (ITMs) which are not themselves devoid of problems. There are already reports of incipient pyrethroid resistance in isolated *Anopheles gambiae* populations. The greatest technical challenge to malaria control in Africa however is the emergence, intensification and spread of anti-malarial drug resistance, sweeping across tropical Africa. As we learned in previous presentations, formerly trusted anti-malarial drugs are in some countries already being abandoned.

The predicament inherent in the above malarial control failures dictate for the search of more effective malaria control tools. Malaria vaccines, in the African context are seen as the promised new tools, mainly because malaria vaccines, like other vaccines in public health use, are likely to be affordable, cost-effective, relatively easy to administer and maintain, acceptable, effective and sustainable in poor-prone African communities. The rest of this presentation will review past African experiences with malaria vaccines, outline the lessons that were learned, and set out future perspectives.

Experience with Malaria Vaccines

The fact that inhabitants of malarious areas, who get frequently bitten by malaria infective mosquitoes, do not always develop clinical malaria led scientists to believe that these individuals develop an effective immune response. Later studies showed that laboratory animals could be effectively immunized with irradiated sporozoites (Nussensweig *et al,* 1967). Soon after, it was shown that humans could be similarly protected (Clyde, 1973).

There were however major drawbacks with immunizations with whole parasites. Over the last decade considerable research has therefore focused on sub-unit malaria vaccines. Such research endeavours have resulted in the identification and isolation of purified antigens, which have been shown to induce strain specific immunity in laboratory animals.

Such achievements are, however, merely preliminary indicators of possible protection in humans. To develop an effective malaria vaccine that is applicable in public health intervention programmes demands considerable clinical and field evaluations beyond laboratory models.

By the late 1980s, there were very promising results from early clinical trials in humans, of recombinant or synthetic malaria vaccine candidates (e.g. Ballou *et al*, 1987, Herrington *et al*, 1987; Patarroyo *et al*, 1987, and Patarroyo *et al*, 1988). Following on from these findings, a number of fields trials were made in several African countries using vaccines carrying components of the circumsporozoite (CS) protein. A meta-analysis for the Cochrane Collaboration was carried out by P. Graves (1997) on field trials in Nigeria, Burkina Faso, Kenya and Thailand, which were random and placebo-controlled, (Reber-Liske *et al*, 1983; Sherwood et al, 1996). Graves concluded that there is no evidence for a reduction in the incidence of malaria by sporozoite vaccines.

New CS based vaccines are meanwhile being developed; some utilizing new adjuvants. In this regard, Stoute *et al* (1997) protected six out of seven naïve volunteers against *Plasmodium falciparum* sporozoite challenge. These promising results were followed, by on going field trials in the Gambia; a preliminary report on initial attempts appeared in the AMVTN Newsletter (1997a). This Conference will learn more on this study. I understand a similar study is underway in Kenya.

Transmission blocking vaccine candidates have been isolated and purified. Some have undergone laboratory testing. The furthest developed vaccine candidate in this category, Pf25 is still undergoing early clinical testing for safety and immunogenicity in the USA and elsewhere. Preparations of field study sites in several African institutions are underway.

Trials of asexual blood stage vaccines have made greater inroads into Africa. Although there are many antigens in this category (e.g. MSP-1, MSP-2, RESA, AMA), only SPf66 has experienced wide-ranging clinical and field testing not only in Latin America, its continent of origin, but also in Africa, and to some extent in Asia (Thailand). SPf66 is a chemically synthesized vaccine against *P.falciparum* , designed and developed by Dr. Manuel Patarroyo in Bogota, Colombia. In preclinical trials, SPf66 induced significant protection against blood challenge in *Aotus* monkeys (Patarroyo *et al,* 1987) and later in humans (Patarroyo *et al,* 1988). In a properly designed field study Valero *et al* (1993) showed a significant reduction in clinical malaria under natural exposure in Colombia. Studies in several Latin American countries obtained similar data, although they were often not well designed.

The Latin American results stimulated intense discussion in scientific circles. A major challenge to SPf66 was thought to be Sub-Saharan Africa, particularly in areas of intense year round transmission. If SPf66 worked under such situations, it would be expected to work elsewhere. Other supplementary, yet crucially important questions were then raised which queried whether SPf66 could lead to undesired immuno-modulation (suppression or pathology) in populations subjected to constant malaria challenge, and whether the protection was peculiar to Latin American *Plasmodium falciparum* strains, as opposed to African strains. The first study on SPf66 undertaken outside Latin America was done in the Kilombero Valley in Tanzania from 1991 to 1994. Results from the initial Tanzania studies involving 586 children 1-5 years of age, showed SPf66 to be safe and immunogenic

(Teuscher *et al*, 1994) and partially effective, giving an estimated efficacy of 31% against first malaria episode. There was however wide 95% confidence intervals (Alonso *et al*, 1994 and Tanner *et al*, 1995). In a follow up study at 18 months after the third dose, the vaccine efficacy was estimated at 25% (95% CI=1-44); there was therefore prolonged protection (Alonso *et al*, 1996) although, again, the confidence interval was still wide.

The above SPf66 study was in young children, although in areas of intense year round malaria transmission, as in the Kilombero valley, the brunt in terms of disease and death is most intense during infancy when much of the malaria is acquired. It was therefore logical to now test SPf66 in infants through the expanded programme of immunization (EPI), with the view of determining its safety, efficacy and interaction alongside standard EPI vaccines. In results just to be published there were no serious adverse effects (Schellenburg *et al*, in press), the vaccine was immunogenic, did not interfere with the EPI vaccines, but only gave an estimated efficacy of only 2% (Acosta et al, in press). The authors therefore concluded that SPf66 in its current alum based formulation, does not appear to have a role in malaria control in Sub-Saharan Africa; they also caution of difficulties in inducing protective immunity against malaria through immunization of infants.

A prelude to the Tanzania study was one *in* the Gambia which, however, differed from the Tanzania study in the age of the study subjects, the period of follow up, and the highly seasonal malaria transmission. The Gambia study showed no statistically significant difference in efficacy, admissions or mortality between the vaccine and placebo group (D'Alessandro *et al* 1995).

In summary, up to now neither of the three malaria vaccine types (sporozoite, sexual or asexual blood-stage) have proved efficacious under field test conditions in Africa. There is therefore need to go back to the drawing boards.

Lessons learnt

Despite failures in producing a highly efficacious malaria vaccine for early deployment in African public health settings, many lessons have been learnt. The last two decades have witnessed considerable progress in the understanding of immune mechanisms that are involved in conferring protection to malaria, the identification of vaccine candidate antigens and their genes, followed by the demonstration of protection in experimental animals.

Early studies demonstrated that humans residing in malaria endemic areas in Africa acquire natural immunity over time. Moreover, experimental vaccination with attenuated sporozoites (e.g. by irradiation) provide effective protection. Unfortunately such an approach would be unwieldy, and would not be technically and economically feasible. Much investment over the last two decades has therefore focused on recombinant or synthetic sub-unit vaccines.

Experience over this period has confirmed that development of malaria vaccines presents formidable difficulties. The encountered complexities relate mainly to the complex malaria parasite biology, human immune responses, pre-clinical, clinical and field vaccine evaluation. It is, for example, becoming abundantly clear that not only do humans possess complex heterogeneities, but parasites and vectors are also just as complex. To this should be added the external and internal milieu. The picture is further complicated by the

complex malaria life cycle, with parasites going through particular developmental stages, each with almost unlimited antigens, only some of which might constitute future vaccine candidates. Then there are likely differences in vaccine batches and their formulations.

At the pre-clinical level there is still lack of good laboratory model systems for human malaria, although the blood stages of the *P.falciparum* can be conveniently cultured.
Similarly, at the clinical level assessment of the efficacy of a candidate vaccine is still problematic. With pre-erythrocytic vaccines one can directly measure parasitaemia after sporozoite challenge, but this is not the case with asexual blood stage vaccines. To me, this constitutes an ethical dilemma. In different areas of endemicity, and in different levels of pre-exposure, there is no level of parasitaemia constituting an agreed end point. Indeed the entire issue of case definition of protection for malaria vaccines in field trials is still unclear, and calls for further elucidation.

Despite considerable research output in basic and developmental malaria vaccine research, the same cannot be said of clinical trials. Of the many antigens developed from basic and pre-clinical research, only a very small proportion ever enter early clinical assessment to say nothing of field testing. To put it rather bluntly progress from the laboratory to the clinic has for the most part been slow if not disappointing. Even where vaccines have entered full field evaluation they seem to reach a dead end, at least with certain formulations, certain age groups, or certain levels of malaria endemicity. To put it mildly “many are called (but only) a few are chosen”.

The current impasse with SPf66 studies, particularly in infants, point at yet more and greater hurdles to be overcome. Success in Phase III testing does not provide a readily available public health tool. Further testing, particularly for compatibility with EPI vaccines and their administration is an absolute necessity.

An examination of the studies reviewed shows that we have indeed come a long way, despite the hurdles. In only a few years there has been great improvement in malaria vaccine field study designs; random, double blind, placebo controlled studies are now the norm, rather than the exception. During this short period, a level of understanding of a critical path and sequence of trials also seems to have been reached.

Future Perspectives

There is no doubt that there is considerable malaria research based on *in vitro* systems and on animal models. Since these do not fall under this presentation, it is assumed that they will continue, and they indeed need to continue and intensify, so as to provide more candidate vaccines.
I would hazard to say that there is pressing need for new malaria research investment focusing on clinical and field research. Such investment should, besides testing malaria vaccine candidates, examine areas that may in one way or another constitute limitations to malaria vaccine development. For example, studies of pathogenesis, or of correlates of protection that will be useful in future efficacy trials.

If future malaria vaccine field trials are to bear fruit that will endure, research capacity in malaria endemic areas should be adequately strengthened so as to reduce the gap between basic research institutions in the north and African field trial institutions. Particular attention should be given to institutions that are likely to participate in malaria vaccine

trials. This aspect will be addressed in another session. At this point I must stress that capacity building should be all inclusive of human resources, infrastructure, supplies, etc.

Human resources development deserves utmost attention. A recent survey (AMVTN 1997b) shows a critical shortage of appropriately qualified African researchers across the board, ranging from the traditional biomedical areas of molecular biology and immunology, all the way to specialties that are crucial in the field evaluation of malaria vaccines and other interventions (e.g. epidemiology, public health, health economics, behavioural sciences and the like). Furthermore, human resources development, must go much beyond training in these traditional areas; training in skills such as good clinical/laboratory practice, study and protocol design, data management and ethics should also be provided. Continuing education of African malaria researchers is essential, given the intellectual isolation they experience.

Meanwhile as new vaccine candidates are being developed, future malaria vaccine testing sites should be better characterized. Detailed information should be gathered on malaria epidemiology, transmission dynamics, pathogenesis, heterogeneity of parasites, vectors and human hosts, spectrum of responses to antimalarial drugs and the like. We shall also need to characterize the type and magnitude of host immune responses in pathogenesis and resistance. These will concern:

- endpoints, surrogate markers, case definition.
- development and validation of field methods for sub-clinical malaria infections.
- establishing repositories of well characterized parasites, vectors, genetic probes, antibody reagents.

There is greater need than ever before to establish working partnerships and networks. In this regard future trials should, whenever possible, be guided by the recently developed WHO guidelines. In order to ensure comparability, multi-centre trials will be desirable, whereby different eco-epidemiological and endemicity settings will be involved. Besides sharing common protocol designs, the participating centres would also share experiences, operational burdens and results. Co-ordination in planning and executing trials is crucially important. Greater involvement of mechanisms as provided by the African Malaria Vaccine Testing Network is highly desirable.

The flow of information on planned or ongoing malaria vaccine trials is at best a mere trickle. In many cases, only research teams know the research plan and its progress. Isn't there need to divulge such aspects as rationale, design and methodology well ahead of the study results?

Conclusions

Although there is ample evidence from field observations and experimental studies that vaccination against malaria is feasible, the development of a safe, efficacious and cost-effective malaria vaccine that can be deployed within the Expanded Programme on Immunization, in an area in Africa experiencing intense perennial malaria transmission, is still evasive. According to this review, SPf66 has failed the rigorous test; RTS.S is still racing ahead, whereas new vaccines including DNA vaccines and new adjuvants are entering the scene. A Luta Continua.

The process involved in pre-clinical, clinical and field-testing is long, demanding and very expensive. The first SPf66 study in Tanzania cost almost US$1 million. It is therefore not likely that a malaria vaccine will be deployed in Africa in less than ten years from now. Given the above realities, malaria control in Africa should continue to rely on available strategies involving chemotherapy or chemoprophylaxis and vector control.

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Basic Research on Malaria Vaccines

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In thinking about standing up in front of the individuals in this audience, many of whom are involved in malaria control, I was struck by the thought that many of you would think, "Here we go again, another talk about malaria vaccines. We've been hearing about these imminent vaccines for fifteen years. There always seem to be fabulous high tech advances, but things don't seem to change very much, and we still don't have a vaccine." The fact is that we don't have a vaccine. However, I hope that all of you will leave this room with some of the enthusiasm and perspective that I have for the tremendous advances that have been made in the past few years in the field of malaria vaccine development, and with some of my confidence that this work is bringing us much closer than we have ever been to fielding an effective malaria vaccine.

To try to put malaria vaccine development in context, I would like to draw upon several of the points that have been raised repeatedly during this meeting. One has to do with the clinical epidemiology of malaria. I believe that 10-15 years ago if I asked any of you who were working on malaria, what the major clinical manifestation of severe disease leading to death in children in the areas with the most intense transmission of malaria was, you would have told me, as I would have told anyone, that it was cerebral malaria. In this meeting, we have heard over and over again, that it is probably severe anaemia not cerebral malaria. In fact cerebral malaria may not be very common in young children in the areas with the most intense transmission of malaria. Likewise, 10-15 years ago, if asked what age group of children contributed most to the mortality of malaria, I think it would have been unlikely for anyone to have said infants. The common wisdom was that infants were protected by maternally transferred immunity. However, it is now estimated that in some areas with intense malaria transmission, 25%-50% of malaria-related deaths occur in children less than 8 months old.

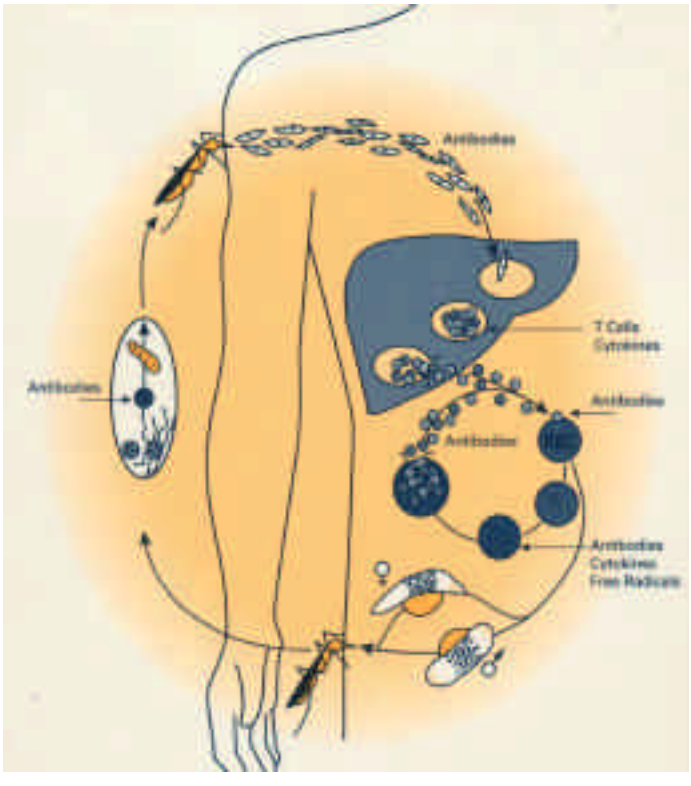


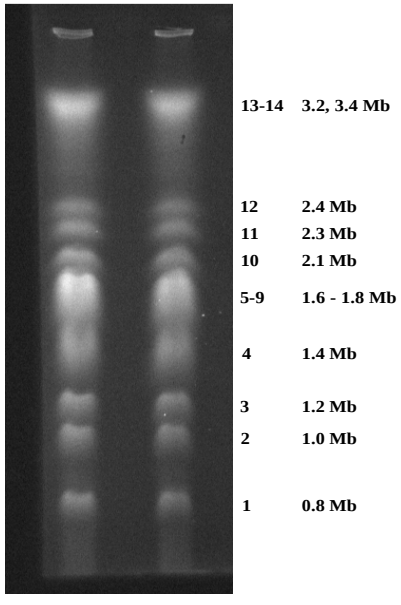
Figure 1: The life-cycle of the malaria parasite

Lastly, how many molecular biologists are in the audience? How many of you would have believed me if I told you two years ago that in the *Plasmodium* falciparum genome there is probably a family of genes encoding variant surface proteins with an estimated 2-2.5 times more copies than Var genes? I think that no one would have believed me. However, in one

fell swoop the genomic sequence data from chromosome 2 of *P. falciparum* has raised that possibility. My point is that if one considers how incomplete our understanding of the clinical epidemiology, immunology and molecular biology of *P. falciparum* was 5-10 years ago, it is not surprising that we have not made the rapid progress in vaccine development that we had hoped for. Specifically, why isn't there a malaria vaccine after so many years? One reason is that we are faced with a formidable foe. We have a complex parasite, which has a multi-stage life cycle, and stage-specific expression of proteins. That means that if a protein on the surface of sporozoites is a major target for antibodies, even if we elicit high levels of anti-sporozoite antibodies, those antibodies will generally not recognize the blood-stage of the parasite's life cycle!

Furthermore, *P. falciparum* has a large genome of 30 megabases on 14 chromosomes (Figure 2) and an estimated 6,000 genes. And the parasite has allelic and antigenic variation. In regard to allelic variation, we know that a single individual can be infected with more than five different strains of *P. falciparum* .

Figure 2: Fourteen chromosomes of *P. falciparum*



Another reason why it has been difficult to develop vaccines is that the human response to the parasite is quite complex. This response is in large part a reflection of the human host's genetics, the transmission dynamics of the parasite, and perhaps even the age of the host. We all know that individuals with sickle cell trait generally do not develop severe malaria. Recently it has been suggested that certain genetic characteristics make one more susceptible to severe disease. However, the fact is that we may actually know very little about the relationship between host genetics and the response to infection. I am hopeful that the elucidation of sequence of the human genome and the development of scientific tools to use these data will lead to a much better understanding of the role of host factors in determining the severity of disease associated with infection. Immune responses are also dependent on transmission dynamics. In areas where transmission of *P. falciparum* is most intense, infants are at highest risk of developing severe and fatal malaria. In areas with less intense transmission, older children have a higher incidence of severe and fatal disease than do infants. The age of the individual may also be important. A number of reports have suggested that among non-immune children and non-immune adults, the adults are actually more susceptible to developing severe disease after their first infection than are children. However, the adults develop acquired immunity faster than do the children. We have much to learn about the impact of host genetics, transmission dynamics, and age on the pathogenesis and clinical manifestations of malaria.

There are currently three general approaches to malaria vaccine development being pursued. The most work has been done and progress achieved on an approach focused on maximizing the magnitude and quality of immune responses to a single or a few key antigens, such as the circumsporozoite protein (CSP) and merozoite surface protein 1 (MSP1), by immunizing with synthetic peptides or recombinant proteins in an adjuvant. These vaccines are being designed to primarily induce antibody and $CD4^+$ T cell responses, but there is also interest in eliciting $CD8^+$ T cell responses. The second

approach is to induce good or optimum immune responses against all of the approximately 15-20 identified potential targets proteins by immunizing with DNA vaccines and boosting with either DNA vaccines, recombinant viruses or bacteria, or recombinant proteins in adjuvant. The goal is to elicit antibody, $CD4^+$ T cell and $CD8^+$ T cell responses. The third approach is to try to duplicate the whole organism immunity induced by immunization with radiation attenuated sporozoites and natural exposure to malaria. Success in this area will be dependent on the sequencing of the *P. falciparum* genome and developing methods for exploiting this genomic sequence data. It remains to be established how such vaccines will be constructed.

Many malariologists believe there may not be only one malaria vaccine. I am not certain I'm amongst them, however, I find it very useful to think about the extremes of requirements for a malaria vaccine. One requirement is to reduce malaria associated mortality and the incidence of severe malaria in infants and children in Africa. There has been considerable discussion at this meeting regarding how to do this. The other extreme requirement is to prevent all clinical manifestations of malaria in individuals from areas with no malaria who travel to areas with malaria.

Children living in Navrongo in northern Ghana are frequently infected with *P. falciparum* , and when infected develop a febrile illness that prevents them from playing or going to school. However, they rarely, if ever, develop severe disease or die of malaria. Essentially all the deaths in this region occur in the first 1-2 years of life. In Navrongo there is a single hospital that serves the approximately 175,000 residents of Navrongo as well as residents of neighboring areas. In 1996, 41% of deaths in the hospital were attributed to malaria, and another 18% to anaemia. Since much of the anaemia can be attributed to malaria, this suggests that 50% of all deaths in the hospital were caused by malaria. We would like to have a malaria vaccine that, from an immunological point of view, turns 6 months olds into the 4 or 5 year olds in the picture. In other words, a vaccine that prevents death without necessarily preventing infection or even mild illness.
Saradidi is a place in western Kenya, where the transmission intensity of malaria is similar in many respects to the transmission intensity in northern Ghana. It is not infrequent for someone born in western Kenya to attend university in Nairobi, and then get a job, get married, raise a family, and settle in Nairobi where there is no malaria transmission. The children of these Nairobi residents are non-immune to malaria. When they visit their families in western Kenya on school holidays they are at high risk of contracting malaria and rapidly developing severe disease. There is very little mention in the malaria literature of the increasing numbers of non-immunes living in countries with endemic malaria who must receive short-term protection against malaria by a vaccine. Because of their susceptibility to rapidly developing severe disease, because they will not have the repeated exposure that could lead to boosting of vaccine-induced immunity, and because they are only visitors, I would think that their parents would want them to have a vaccine with the same preventative profile as a vaccine required by travelers from North America or Europe. What would you choose in that setting?

So, in thinking about developing a vaccine, and the target population for a vaccine, we need to think about the patterns of morbidity and mortality. We desperately need much more sophisticated information regarding the epidemiology of severe malaria and malaria associated mortality. I hope that many of you will return home, and begin to systematically collect the epidemiological data that will be critical to designing malaria vaccine trials. If the majority of deaths from malaria in an area are in 6-12 month old infants, we would be foolish to do a vaccine trial in 2-4 year olds. Likewise, if the majority of deaths are in 2-4

year olds, data on vaccine efficacy will be acquired most rapidly if we vaccinate 1-2 year olds, not newborn infants. Furthermore, if certain groups in the population almost never die of malaria because of the genes that they have inherited, then it makes no sense to include them in a vaccine trial aimed at determining whether a vaccine reduces mortality.

We think that in northern Ghana it is infants who are primarily dying of malaria and we think that in the Gambia it may be 2-5 year olds who are primarily dying. Why do they die? It appears that in northern Ghana severe anaemia caused by malaria may be the major cause of death and in the Gambia, cerebral malaria. Is it possible that we may need different vaccines for infants who die of severe anaemia and for older children who die of cerebral malaria? I certainly do not know the answer to that question, but I do know that I need to understand the epidemiology of malaria in the area if I am going to adequately design a vaccine trial to try to reduce the major cause of death in that area. Data from the large studies with insecticide impregnated bednets could be very helpful in this regard. Those studies showed 18% to I believe approximately 50% reduction of all-cause mortality. Who were the individuals whose lives were saved? My recollection from reading some of these studies is that the reduction in risk was not significantly different in infants or children up to the age of five or so. However, since the infant (1-11 months) and even 12-23 month old mortality rate was up to 4 times higher than the mortality rate in older children, the numbers of deaths saved in the younger age groups was significantly higher than in the older age groups. A more detailed analysis of these data may provide information that could be enormously helpful in optimally designing malaria vaccine trials.

We actually have human models for the two extremes of vaccines I mentioned earlier. In regard to a vaccine to prevent death and severe disease, we know that naturally acquired immunity is the model. If you make it past a certain age in the areas where malaria is transmitted, you will become reinfected and you will become clinically ill, but you will not develop severe disease or die. In regard to a vaccine to prevent all manifestations of malaria, we have immunization with radiation-attenuated sporozoites. Exposure of humans to the bite of greater than 1000 irradiated mosquitoes carrying *P. falciparum* sporozoites in their salivary glands over 4-6 months protects virtually all recipients against exposure to 5 infected mosquitoes 2 weeks after the last dose of irradiated sporozoites. The protection is not strain-specific and lasts for at least 9 months.

The data included in this figure (Figure 3) were generated in 1986 in Saradidi in western Kenya. Almost identical data have been generated recently in a study in Navrongo in northern Ghana. When adults who have lived their entire lives in areas with intense transmission of malaria are radically cured of malaria, virtually all of them become reinfected within 4-6 months. Naturally acquired immunity is not a model for the vaccine to prevent all clinical manifestations of malaria in travelers, because naturally acquired immunity does not prevent the development of blood stage parasitaemia. In fact, in the recent study in northern Ghana, at the time of identification of parasitaemia approximately 30% of the adults were symptomatic. However, the rate of developing recurrent infections and the parasite densities of recurrent infections are much lower in the adults than in their young children, and none of the adults develop severe disease. However, this data clearly demonstrate that naturally acquired immunity is not a human model for a vaccine for travelers designed to completely prevent blood stage parasitaemia and the clinical manifestations disease.

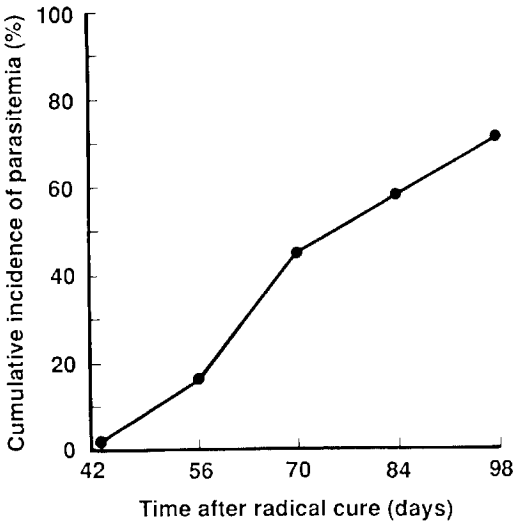


Figure 3: Rate of *P. falciparum* reinfection in Saradidi

The "modern" approach to vaccine development is to identify the mechanisms of protective immunity in the human model system; to identify the antigenic targets of the protective immunity in the model, and then to develop a vaccine delivery system that induces the required immune responses against the identified targets. There are very few vaccines that have been developed this way, and none against any infectious agent as complex *as Plasmodium falciparum* .

What do we know about immunizing with the irradiated sporozoites? First of all, essentially everyone who is immunized properly is protected. This means there is no genetic restriction of protection. The protection is not strain-specific. Individuals immunized with parasites from Africa and challenged with parasites from South America are protected. Protection lasts for at least nine months. The irradiated sporozoite vaccine would be an ideal vaccine for travelers. However, it is totally impractical to conceive of immunizing hundreds of thousands of people by the bites of thousand of infected mosquitoes. Thus, there has been considerable work over the last 30 years to understand irradiated sporozoite-induced protection, and develop a subunit vaccine that duplicates this excellent immunity. We believe that the primary protective immune mechanism in the irradiated sporozoite model involves $CD8^+$ T cell recognition of parasite-infected hepatocytes. However, antibodies and $CD4^+$ T cells almost certainly also play a role in the protection. The targets of the $CD8^+$ T (and $CD4^+$ T cells) are parasite proteins expressed by irradiated sporozoites within hepatocytes. However, sporozoite surface proteins are also the target of inhibitory antibodies.

With pre-erythrocytic stage vaccines we are trying to prevent sporozoites from entering hepatocytes, or developing within hepatoctyes. The irradiated sporozoite vaccine does not elicit immune responses against the major merozoite surface proteins. However, strictly speaking, a pre-erythrocytic stage vaccine could also be designed to elicit antibodies that recognized proteins on the surface of merozoites released from hepatocytes, and thereby eliminate the parasites that may have made it through the anti-sporozoite, and anti-liver stage blockage described above. If parasites actually do invade erythrocytes and begin the process of development, I believe that they will cause disease.

There are quite a few human studies planned or in progress for pre-erythrocytic *P. falciparum* vaccines. We heard extensively yesterday about RTS,S which has been developed by SK BIO (Smith Kline Biologicals) in Belgium, in collaboration with the Walter Reed Army Institute of Research (Stoute *et al.* 1997). We also heard about studies in progress or planned in which RTS,S is being combined with TRAP (also known as PfSSP2). There is a branched chain multiple antigenic synthetic peptide vaccine based on the repeat region of the *P. falciparum* circumsporozoite protein (PfCSP) which has been developed by New York University and the University of Geneva and is being tested in clinical trials at the University of Maryland. There is also a carboxy-terminal synthetic peptide from the PfCSP developed at the University of Lausanne which is in Phase I clinical trials now. At the Naval Medical Research Center (NMRC), we have conducted a

Phase I safety and immunogenicity clinical trial of a PfCSP DNA vaccine, and are planning another trial next month. Next November, we plan to initiate a trial of a 5 gene pre-erythrocytic stage DNA vaccine that includes genes encoding 5 proteins expressed by irradiated sporozoites in hepatocytes. This project is called MuStDO 5.1 (Multi-Stage Malaria DNA Vaccine Operation-5 gene, iteration 1). This is collaboration between NMRC, Vical Inc., the United States Agency for International Development, the Institute Pasteur (Paris), and Pasteur Merieux Connaught. At Oxford, they are going forward in clinical trials with a *P. falciparum* pre-erythrocytic stage multi-epitope vaccine; recipients will receive the first dose as a DNA vaccine, and the second dose as a recombinant attenuated vaccinia virus (MVA) expressing the same epitopes.

There is considerable hope for these pre-erythrocytic vaccine approaches, certainly for the second indication I described, which is preventing all manifestations of the disease. However, there has been quite vigorous debate as to whether a pre-erythrocytic stage vaccine on its own would reduce mortality in children in Africa. If such a vaccine were perfect, it certainly would be effective in this regard, because there would not be any parasites escaping from the liver into the blood stream. If it were less than perfect, most scientists believe that there would have to be substantial anti-asexual erythrocytic stage immunity in recipients. The fact of the matter is that most of the individuals, including infants, that we contemplate immunizing will have some degree of anti-asexual stage immunity. A question that has been raised for which there is no answer is, "What will happen if such a vaccine is perfect or almost perfect for a year or more, and then rapidly becomes ineffective?" Will overall malaria morbidity and mortality worsen since recipients would not have developed anti-erythrocytic stage immunity? We know that the clinical presentation of disease varies in relation to transmission intensity. Others (Snow *et al.* 1997) have wondered if by changing the host-parasite dynamic interactions will we alter the pathogenesis of disease, and in some cases make things worse? There are no answers to these questions, and prospective studies will have to be designed to address them. However, I am encouraged by the fact that preliminary reports from long term studies of insecticide impregnated bed net studies are not finding any delayed increase in morbidity or mortality. One could even characterize insecticide impregnated bednets as being analogous to "leaky" pre-erythrocytic stage vaccines.

The other human model for vaccine development is naturally acquired immunity. In areas with annual, stable transmission, there is little to no severe disease or malaria associated deaths after the age of 7-10 years. In areas with the most intense transmission, the transition to this immunity against severe malaria occurs even earlier, perhaps during the second year of life. Even adults become infected and develop symptoms attributed to malaria, but the incidence of new infection, and the density of parasitaemias decreases with age. Most malariologists believe that antibodies against parasite proteins expressed on the surface of infected erythrocytes and merozoites and in apical organelles play a central role in this naturally acquired disease modulating immunity (Figure 1). However, biologically active molecules including cytokines, nitric oxide, and free oxygen intermediates, either released from $CD4^+$ T cells after an antigen-specific interaction, or released from reticulo-endothelial or other cells after non-specific activation also probably contribute to this immunity. Furthermore, the pathogenesis of the disease itself may be mediated by these same host-derived biologically active molecules, perhaps elicited by putative toxins released from the infected erythrocytes. Antibodies against these toxins may contribute to naturally acquired immunity. Finally, it seems intuitive that immune responses against

sporozoites or infected hepatoctyes that limit the numbers of parasites that emerge from the liver into the bloodstream must also play a significant role.

An important question for scientists studying naturally acquired immunity is, "How rapidly does naturally acquired immunity to mortality actually develop?" In *Aotus* monkeys, a non-natural host for *P. falciparum* , the first exposure to infected erythrocytes of the FVO strain of *P. falciparum* is almost always fatal. However, most survive the second FVO challenge, and all will survive the third FVO challenge. When patients with neurosyphilis were treated by infection with *P. falciparum* a similar pattern was reported. Recently, there was a report suggesting that in areas with intense transmission of *P. falciparum* , this anti-mortality immunity may develop after only one or two exposures to *P. falciparum* (Gupta *et al.* 1999*)*. I think that data derived from studies further exploring this question will be critical to developing and studying effective malaria vaccines. The data may vary considerably depending on the transmission dynamics and epidemiology of the disease, but we will never know until appropriate field studies are executed.

I mentioned that *Aotus* monkeys re-challenged with the FVO strain of *P. falciparum* rapidly develop anti-parasite immunity. I would like to tell you about a study that was recently completed by Dr Trevor Jones from NMRC, and Dr Nicanor Obaldia from Promed Inc. at the Gorgas Memorial Laboratory in Panama. They exposed *Aotus* monkeys (*Aotus lemurinus lemurinus*) 8 times to *P. falciparum* infected erythrocytes. After the first infection with 10,000 FVO-infected erythrocytes parasites, 8 of the 8 monkeys became infected, the pre-patent period was 8.2 days, the maximum parasite density was 840,000 parasites/µl, the geometric mean density being 443 parasites/µl and all of the monkeys had to be treated or they would have died. With their second exposure, 8 of 8 become infected, the pre-patent period lengthened to 12 days, the maximum parasitaemia was reduced by approximately 50%, the mean peak parasitaemia was reduced by approximately 75% to 107,000 parasites/µl and only 5 of the 8 had to be treated. With their third exposure, only 6 of the 8 developed detectable parasitaemia, the pre-patent period was 19 days, the peak was 31,000 parasites/µl, the geometric mean was 220 parasites/µl and none of the 8 had to be treated. With their 6th and 7th infections, none of the monkeys developed parasitaemia; they actually had sterile protective immunity against the blood stage of *P. falciparum* . These monkeys with sterile protective immunity were then challenged with erythrocytes infected with the CAMP strain of *P. falciparum* . Six of the 8 became infected, the pre-patent period which had been 30 days after the fifth FVO challenge went back down to approximately 8 days, the peak parasite density was 11,000/µl and the mean was 1,400 parasites/µl and none of the 8 had to be treated. They did not have sterile protection against parasitaemia but were protected against death. However, 2 of the 8 monkeys developed parasite density levels that would have made humans quite ill (approximately 10,000 parasites/µl) and certainly would have caused fever, and these 2 monkeys and a third monkey had a drop in their hematocrits (packed cell volumes) of greater than 50%. I believe that these results are quite instructive. If we are developing a vaccine to reduce mortality, but our outcome variables in early field trials are parasite densities greater than 5,000/µl, fever, or development of anaemia, we may find that a vaccine that would be effective in reducing mortality was discarded before it was tested for this indication.

Thus, it is critical to consider what outcome variables to measure in field trials of vaccines, and what populations to study. A primary goal is to reduce mortality and severe disease. The problem is that initial studies may not measure these outcome variables, and there is the potential for entirely missing (discarding) a vaccine because we did not measure the proper outcome variable(s). It will be difficult to use severe disease and death as the

primary outcome variables in initial studies, because this would require very large sample sizes. Acquiring data that will allow us to reduce sample sizes by focusing only on groups at highest risk will be enormously important in the future. Some groups are working on identifying surrogates of severe disease and death, parasitological, hematological, biochemical, or clinical manifestations that are predictive of severe outcome. This will not be easy and may ultimately be unrewarding if the surrogate markers occur only in those who will develop severe outcomes as this would not allow a reduction in sample sizes.

There are a number of human trials planned or in progress of erythrocytic stage *P. falciparum* vaccines. Yesterday we heard about recent studies of SPf66. The group in Ifakara, Tanzania in collaboration with the Swiss Tropical Institute and the University of Barcelona have been conducting studies in Tanzania. The Institute of Immunology in Bogota is also conducting studies with SPf66 and other synthetic peptide vaccines. There is a study in progress in Papua New Guinea in which purified recombinant proteins based on three blood stage *P. falciparum* proteins are being studied in the field. There are also several Phase I studies of purified recombinant Pf MSP1 being planned in the United States.

I would like to tell you about a project called MuStDO 15.1, referring to the first iteration of a 15 gene approach to malaria vaccine development. MuStDO 15.1 includes DNA plasmids expressing the 5 genes that encode proteins expressed by irradiated sporozoites in hepatocytes, the plasmids from MuStDO 5.1. It also includes 10 genes encoding proteins expressed on the surface of merozoites or in the apical organelles. The hypothesis is that the pre-erythrocytic stage component will reduce the number of parasites emerging from the liver, and the blood stage component will prime the recipients' immune systems to the 10 erythrocytic stage antigens. Parasites emerging from the liver or from the first few cycles of the erythrocytic stage will boost these primed immune responses, and these boosted responses will limit replication of parasites from this infection, and thereby limit development of severe disease and death. These boosted responses will also limit replication of parasites from the next infection.

The only vaccine delivery system that we have available to us right now for doing this is DNA vaccines. Last year Sir Gus Nossal, chair of the Scientific Advisory Group of the Children's Vaccine Initiative wrote in Nature Medicine, "As arguably the most powerful development of all, DNA vaccines have made their explosive entry, possibly signaling a revolution in vaccinology based on their ease of production, stability and simplicity of combination." He didn't say anything about the immunogenicity of DNA vaccines, but rather stressed their simplicity which should allow for building the kind of complex vaccines that we think that we will need for malaria. In fact our work, and that of others indicate that DNA vaccines on their own are not the optimal way to induce any immune response. That doesn't mean that they won't be adequate; only clinical trials will provide the answer to that question. However, I believe that we must do better and while we are trying to improve the simple, naked DNA approach, we and others have moved toward a prime boost approach that is dramatically more immunogenic and protective than is DNA vaccination on its own.

Incorporating this complexity into a vaccine for humans requires a step by step approach starting with the simplest formulations and progressively making them more complex, if only for safety reasons. Our current work is in part based on some preliminary findings from a clinical trial that we conducted last year. In this study we showed that a DNA plasmid expressing the PfCSP was safe and well tolerated in volunteers (Wang *et al.* 1998). Furthermore, it elicited a $CD8^+$ T cell dependent, genetically restricted, antigen-specific

cytotoxic T lymphocyte response in 11 of 20 volunteers. This was not a malaria vaccine trial, but rather the first demonstration in normal, healthy humans that DNA vaccines were safe, well tolerated, and immunogenic.

We now have an international consortium working on the MuStDO 5 and 15 projects that includes scientists from the United States, Ghana, Australia, France, Panama, Peru and we hope, soon other areas. The cloning of the genes is taking place at the NMRC, Monash University in Australia, and in the case of PfLSA3 at the Institute Pasteur in Paris. Construction of the plasmids is at NMRC and Monash, and manufacturing at Vical Inc. in California. All of the genes used are based on the 3D7 sequence. However, the FVO sequence for PfMSP1 42 is also included.

The plan is to conduct phase 1 safety and immunogenicity trials almost simultaneously in the United States and in Ghana at the Noguchi Memorial Institute of Medical Research. If the vaccines are safe and well tolerated, we hope to conduct safety studies in progressively younger age groups at the Navrongo Health Research Center in Ghana, and do a phase 2a experimental challenge study in the United States, and phase 2b field challenge studies in children in Navrongo. We are hoping to begin the studies by the middle of 2000. We do not know when the studies will be complete, but if all goes extremely well, then we will have the results of the first field trials 4-5 years later. Many argue that there are still too many unanswered questions regarding the immunogens and the strategy, and we should delay initiation until we further refine both. However, we can predict learning a tremendous amount by starting now, but cannot predict what will we have in five years if we don't start now.

Before finishing, I would like to tell you about a third type of malaria vaccine development strategy. This approach is based on the idea of actually duplicating the immunity induced by exposure to the whole parasite (irradiated sporozoites or natural exposure). I have described to you an approach based on optimizing immune responses to 1, 2 or 3 of the proteins encoded by the estimated 6,000 genes in the *P. falciparum* genome, generally by a combination of recombinant protein or synthetic peptide and adjuvant. A second approach utilizes most of the known targets of protective immunity, and attempts to induce good immune responses against 15 of the proteins encoded by the 6,000 genes in the parasite genome, through DNA-based immunization. However, our human models are immunization with the whole organism either by natural exposure or by exposure to radiation attenuated sporozoites. It is possible that the strength of the immunity induced in these settings is dependent on immune responses to hundreds or thousands of parasite proteins. How do we get at this approach? There is currently a project to sequence the entire *P. falciparum* genome. The results of 3% of the genome have been published (Gardner *et al.* 1998), but we expect the complete sequence in 2-3 years. The question to grapple with now is how to adequately assess the thousands of new proteins to be identified in the genome project for potential inclusion in vaccines. We have proposed a strategy (Hoffman et al. 1998), and unfortunately I don't have time to go into it today. Nonetheless, I want to mention that I believe the integration of microbial and human genomics with molecular and cell biology, immunology and epidemiology in the next century will provide many of the answers to the questions we have been struggling with for so long.

In parallel, and perhaps more immediately, I think that several areas of field research could provide data that would substantially facilitate vaccine development. The most important is the identification of target groups for vaccines. As pointed out earlier these will differ from area to area. It is easier to immunize children than infants. Thus, if 2-4 year olds are suffering most from malaria, it does not make sense to immunize infants. To

achieve the most cost effective, efficient studies, it will be best to eliminate those who are not at risk. We need to have the smallest sample size as possible. We need to know if there are other groups, like those with sickle cell trait, who are at decreased risk who don't need to be immunized. We need to at least determine if there are outcome variables that can be measured that have a high predictive value for severe disease and malaria associated mortality. We need a more sophisticated assessment of the impact of bednets and other interventions on epidemiology, and the age-specific attributable reduction in mortality. Lastly, we need to develop better assays for predicting protective immunity. This will of course include a much more detailed characterization of the proteins and epitopes on these proteins involved in protective immunity. However, I believe that obtaining fundamental epidemiological data will have more of an impact on malaria vaccine development and design of field trials than will acquisition of immunological data or the mapping of epitopes.

The importance and difficulty of the task that lies ahead of us cannot be underestimated. Thirty seven years ago, malaria was a significant enough problem for the United States along with many other countries to release stamps commemorating attempts to eradicate malaria. That was more or less the same time that President Kennedy vowed to put a man on the moon. Thirty years ago the first man walked on the moon, but we are still a long, long way from eradicating this deadly disease. I believe that development of malaria vaccines will be critical to actually realizing the dream of eradicating malaria.

Recent publications recommended for reading:

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Correlates of Immune Protection: Practical Implications

Christian Roussilhon, Unité de Parasitologie Biomédicale, Institut Pasteur, Paris, France

The ultimate test of a vaccine against *P. falciparum* malaria is its actual effect on human beings. From this basic consideration, we inferred that long term immuno-epidemiological studies are the most appropriate means of understanding the critical characteristics of the interactions between parasite and man, and a prerequisite to the development of a malaria vaccine.

Only extremely well documented situations of clinical resistance or susceptibility to malaria, and associated immune responses to *P. falciparum* parasites in endemic areas, can be expected to give accurate and reliable data. This means, in particular, that only active, daily and carefully planned, controlled and long-lasting investigations in selected endemic areas can be of value. Such investigations are critical if one expects to characterize the essential immune responses involved in the development of protection.

We initially decided to spend time, energy and money in such a study including the active and full time participation of specialists from different origins. The common goal was to understand, analyze and literally dissect every single malaria-related event occurring in Dielmo, a small village of Senegal where malaria is holoendemic. A staff of medical doctors, nurses, and scientists (including epidemiologists, entomologists, and immunologists) was established. This long-term study involved 250 villagers, who were included after informed consent, which was annually renewed. This program was designed so as to accurately identify any single episode of fever and disease whatever their origin, in every family, everyday all year round. In practical terms, this means that highly trained medical staff were permanently stationed in the village itself, ready to handle any complaint of a villager at any time, during day or night. In addition, active detection of symptoms was recorded by daily visits to every single household. Only such a daily visit to each inhabitant can provide a reliable indication of the actual occurrences of sickness in the village. Every month, a capillary sample was obtained from each inhabitant of the village. In parallel, entomological data are recorded every month, all year round.

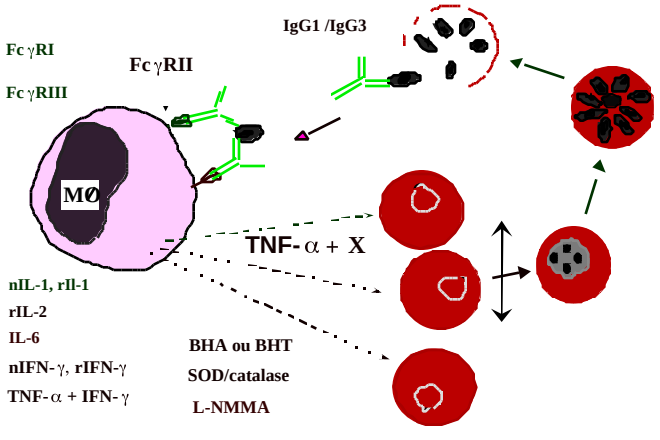
Analysis of the daily data from the first 3/4 years of study allowed us to establish an age-dependent threshold level of parasitaemia associated with clinical malaria. It is our firm conviction, after almost ten years of follow up in this village, that only the conjunction of the permanent presence of a medical staff, the active enrolment of the participating villagers for the daily search for sick persons, and above all, the constant approval of the villagers, guarantee the validity of such data gathering. Hence, we also believe that despite its cost, the acute value and unique quality of epidemiological indications, regularly checked and controlled in this program, offers a trustful basis for determining the clinical status of an individual and allows us to compare biological tests between inhabitants of the village.

The experimental transfer of IgG antibodies from protected Africans to unprotected children has allowed us to better understand how these antibodies act upon the parasite. Of particular interest, is the observation that antibodies reduce parasitaemia, but do not eliminate the parasite (i.e. there is non-sterilising immunity). When tested *in vitro*, immunoglobulins were not inhibitory on their own: antibody-dependent inhibition of *in vitro P. falciparum* cultures was only observed when monocytes were present. Thus,

protective antibodies are apparently acting indirectly by triggering the release of parastatic substances from monocytes. This mechanism, known as antibody-dependent cellular inhibition (ADCI) (Figure 1), operates via cytophilic antibodies only (i.e. IgG1 and IgG3). These original observations formed the basis of detailed field research to evaluate the respective roles of antibody subclasses, in response to parasite antigens in different endemic areas of Senegal.

1) In Dielmo, we found that antibodies against whole blood stage parasites increased with age, and hence with cumulative exposure to *Plasmodium* and decreasing risk of malaria attacks. In a cross-sectional study, the association of antibody responses against parasite antigens and occurrence of malaria attacks was analyzed (Figure 2). This study showed that, of the different antibody classes and subclasses tested, only the IgG3 antibody reactivity was significantly associated with a decrease in the risk of malaria episodes when all known confounding variables were controlled(age, G6PD deficit, AA and AS Hb phenotype). The role of the IgG3 antibody reactivity was more pronounced in young children than in adolescents, and comparatively reduced, but still present, in adult individuals.

Figure 1. The ADCI mechanism



2) On the basis of these initial observations, we then tested the antibody activity detectable in different groups of villagers, differing by their relative susceptibility to malaria attacks. For example, among women, the risk of malaria attacks was increased 4-5 fold during pregnancy. At the same time, we found a drop in IgG3 antibody reactivity against the whole parasite. In a subgroup of children, we found individuals repeatedly suffering from malaria attacks, whereas another subgroup of children of comparable age had no such risk of malaria. In these two situations, parasite-specific IgG3 antibody activity was consistently decreased when the risk of malaria attacks was raised. Therefore, in different situations of susceptibility/resistance to disease, a key role for specific IgG3 antibody reactivity was observed.

3) During the period following delivery (post partum period), a drop in IgG3 was observed for a period of up to 3 months in all women tested. The risk of malaria at this time was significantly increased (around 7 times) by comparison with the risk found in the same women tested one year later, in similar conditions of parasite transmission levels. This was another situation where alteration in IgG3 levels was associated with an increased risk of malaria.

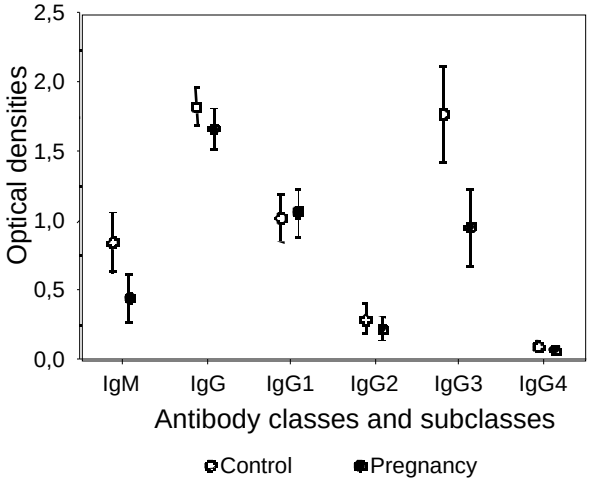


Figure 2. Pattern of parasite-specific antibody activity during pregnancy and comparable control periods in Dielmo

4) The antibody response against different malarial antigens (MSP1, MSP2, MSP3, AMA1, RESA) was then tested in Dielmo. Only the antibody responses against the recently described Merozoite Surface Antigen 3 (MSP3) (Figure 3) were related to protection. In Dielmo, IgG1 and IgG3 responses to MSP-3 increased with age, and hence with cumulative exposure to *P. Falciparum* (see below). The ratio of cytophilic to non-cytophilic antibodies was also evaluated: for each age group (i.e. in an age-independent manner), this ratio was higher for individuals with no malaria attacks than for individuals who had suffered from malaria attacks (Figure 4).

5) IgG3 antibody responses against different antigens (MSP1, MSP2, MSP3, R23, GLURP, SERP) were then tested in cord blood. Different levels of antibodies were detected, and the occurrence of malaria attacks varied between infants. For some children (n= 18), the first detectable infection by *P. falciparum* led immediately to a malaria attack. In contrast, for other children (n= 21), a peripheral parasitaemia was detectable for a mean of 27 days before the occurrence of their first malaria attack. These two groups of infants belonged to mothers with significantly different levels of anti-MSP3 IgG3 antibodies. In this natural situation of parasite-specific antibody transfer, there was a direct association between the transfer of maternal anti-MSP3 IgG3 antibodies and a delay before occurrence of a malaria attack in infants. The *Plasmodium*-specific antibody responses measured in the cord blood were therefore related to resistance to malaria during the first 3 months of life.

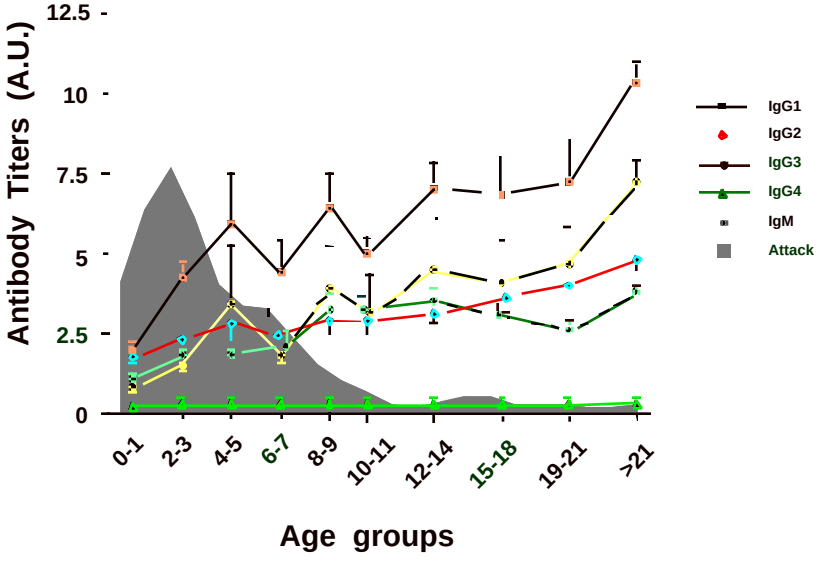


Figure 3. MSP3-specific antibody responses in Dielmo (holoendemic area)

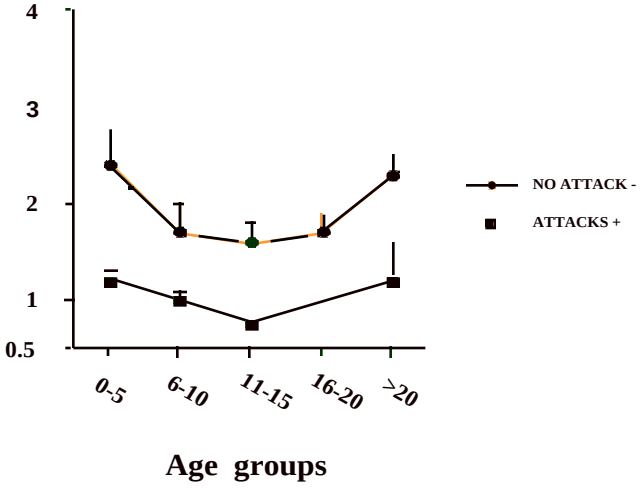
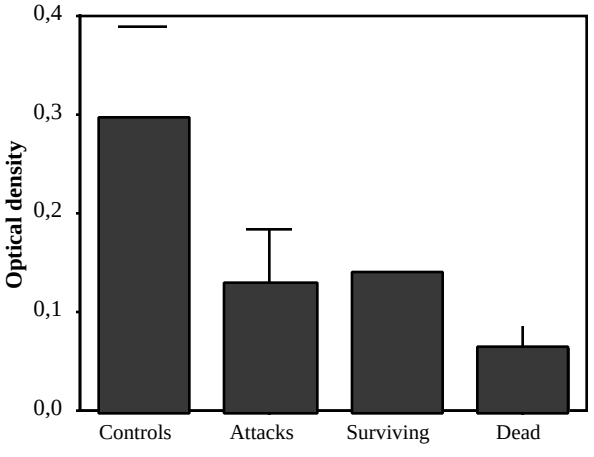


Figure 4. Ratio of cytophilic to non cytophilic anti-MSP3 responses in Dielmo

6) When the antibody reactivities of patients from Greater Dakar with cerebral malaria were evaluated, it was found that the level of IgG3-specific activity was significantly associated with an increased chance of recovery from this life-threatening episode**.** When the antibody response against MSP3 was evaluated, we found three times more IgG3 anti-MSP3 in the subgroup of patients with a propitious evolution as compared to the subgroup with a fatal evolution.

7) Finally, a prospective study was carried out during the low transmission period in a seasonal malaria transmission area (the village of Niakhar) (Figure 5). Blood was obtained on capillary samples from 4,200 children at the time of no malaria transmission. The children were followed up during the following transmission season, when 51 suffered from severe malaria. The level of IgG3 activity directed to MSP3 was found associated with both a decreased risk of severe malaria attack during the following high transmission period, and an improved prognosis following drug treatment in 42 out of 51 severe malaria episodes.

Figure 5. Pattern of antibody activity against the MSP3 antigen in Niakhar (mesoendemic area)



These observations were therefore convergent. They consistently illustrated the association of IgG3 antibody response to antigens of *P. falciparum* and in particular MSP3 with a reduced risk of malaria.

Thus, both immuno-epidemiological investigations and IgG transfer experiments highlights the unique role of cytophilic antibodies in the control of human malaria. This convergence cannot be fortuitous, but most likely reflects one of the mechanisms of defence developed by human beings naturally exposed to *P. falciparum,* and actually involving the participation of cytophilic antibodies.

The mechanism of Antibody Dependent Cell Inhibition (ADCI) is one of the prime potential processes involved in protection against malaria, and more particularly in premunition. The merozoite surface protein, MSP3, was identified by Claude Oeuvray using ADCI as a functional screening tool. Of particular interest, was the fact that MSP3 was also the most readily recognized of the antigens tested in different situations in Senegal. IgG3 activities directed against the MSP3 antigen were found to be critically involved in individuals with a marked protective status. It was not unexpected that an antigen characterized on the basis of its capacity to be a prime target of ADCI (a mechanism associated with an isotype imbalance) was predominantly recognized by cytophilic

antibodies in protected versus non-protected individuals. This was basically an *in vivo* confirmation of *in vitro* data.

The IgG3 activity has been consistently and repeatedly found associated with a markedly reduced risk of malaria attack. This suggests that it could be considered as a prognostic indicator of resistance to malaria attacks in endemic areas. It is a privileged biological marker of protection in different situations of resistance or susceptibility to malaria attack.

In summary, of all the antibodies tested against several erythrocytic stage antigens, only those with a specificity for MSP3 were found significantly associated with a reduced risk of malaria attack. The information initially obtained from the IgG transfer experiment has emphasised a critical role for the co-operation between antibodies and monocytes and led to the identification of the MSP3 antigen. We now confirm in different epidemiological and clinical situations a critical role for the cytophilic antibody subclasses, particularly those directed against MSP3. It is clear that studies on human beings, the natural host of *falciparum* malaria are of utmost value and, despite their huge implications in term of cost and constraints, such approaches probably represent the most rewarding and informative way to gain insight into host-parasite relationships and ultimately efficiently fight this deadly disease. It came as a satisfactory and encouraging result that data obtained from two different lines of research were so strongly convergent and highly complementary. The above studies provide well-established markers of protection in humans and we believe they will be of paramount value in vaccine development.

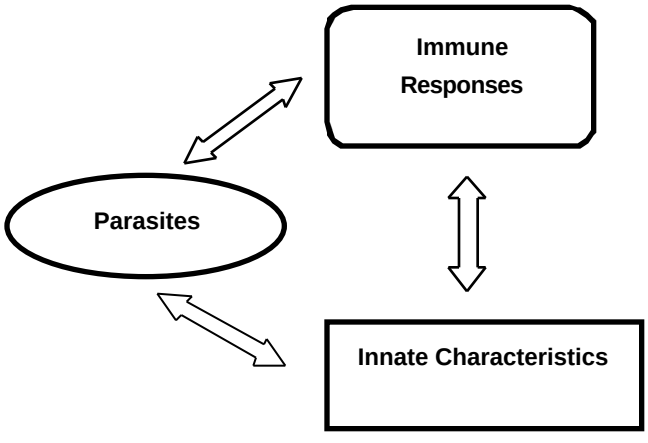
What can we learn from Molecular Epidemiology?

Dr Odile Mercereau-Puijalon, Unité d'Immunologie Moléculaire des Parasites Institut Pasteur, Paris, France

During this talk, I will try to give a brief overview of what we have learnt from molecular epidemiology that is relevant to vaccines, as this was the task that our Chairman assigned to me. The outcome of an infection depends on a complex matrix of interrelated factors (Figure 1):

- The host's innate characteristics, such as genetic susceptibility, age and nutritional status.
- The host's immune response, including the immune status at the time of the infection, and the magnitude and type of response to the infection. This response is crucial in the determining whether immunopathology or protection results and it is dependent upon factors such as previous exposure to *P. falciparum* parasites, on past or current infections and on the age of the host.
- The parasite itself, including its phenotypic characteristics, antigenic makeup and multiplication rate. The actual number of parasites present and the number of distinct genotypes are also important.

Figure 1. Matrix of factors



The respective weight of each parameter is itself strongly influenced by transmission intensity and duration. It makes a difference if you receive all your bites in a two month period or if you get them all over the year. What we are trying to do in molecular epidemiology is to integrate the dimension of parasite characteristics and diversity into the equation. What I shall do now is concentrate on the parasite/immune response, as this is the most crucial aspect for vaccines.

Parasite Diversity

Three major factors contribute to parasite diversity:

1 Allelic polymorphism. Many genes coding for surface antigens, such as merozoïte or sporozoïte surface antigens, show extensive allelic polymorphism. This results in numerous serotypes and T-cell epitope variants within the population.

2 Antigenic variation. The parasite genome has a repertoire of 50 *var* genes, each coding for different serotypes of an antigen exposed on the surface of the infected red blood cell. This results in a phenotypically heterogeneous population of otherwise identical parasites, such that no single infection is homogeneous for its red blood cell surface phenotype. Not only are there 50 *var* genes per genome, but the *var* repertoires within the species are highly diverse, creating a very large population diversity.

3 The sexual cycle. Sexual reproduction in the mosquito can potentially generate novel chromosome assortments, gene combinations and alleles from heterozygous oocysts. The very existence of sexual reproduction in a highly polymorphic species is worrying in the long-term, because it is able to generate an endless source of novelty.

These factors all contribute to diversity of field populations so that parasite isolates can differ in:

- surface antigen serotype
- combinatorial association of surface antigen
- variant antigens expressed at the time of sampling
- their *var* repertoires
- the number of clones present in each isolate.

Molecular epidemiology started long ago, in the 1970's, with the work of Carter, McGregor and Voller. Using isoenzyme typing they discovered several important features concerning *P. falciparum* infections in man, which have been largely confirmed by subsequent molecular epidemiology studies using either monoclonal antibody typing or the more widely used PCR approach.

PCR genotyping

The PCR genotyping strategy has become popular, because it presents several advantages:

- It is very sensitive, much more sensitive than the microscope, allowing analysis of asymptomatic infections.
- It is not restricted by expression stage - with one parasite DNA sample collected from peripheral blood, mosquito or an autopsy specimen you can analyse virtually all genes of the parasite, whatever their stage of expression.
- It generates the material to be studied, instead of using it up as with other techniques, providing the opportunity to study novel alleles by DNA sequencing. So the more PCR you make and sequence, the more you know about diversity.

However, PCR genotyping has its limitations and constraints and is far from a perfect tool. For example, quantification is problematic in isolates with multiple clones, and minor alleles are frequently undetected. It is also at present impossible to discriminate gametocytes from asexual parasites, as they have the same genotype. This is a real issue when one studies the dynamics of infections in man. In addition, PCR analysis concentrates on genotypes without providing any clue on the phenotypic consequences: two alleles with different repeat copy numbers will be typed as genetically different, but will probably express the same serotype. Finally, unlike mAbs, negative parasites are not visualised. If an allele has a mutation in the sequence of the primers, then it will not be amplified and remain undetected.

Cross-sectional studies

Cross-sectional studies allow study of genotypic diversity within parasite populations and individuals, as well as some characteristics of infections such as 'complexity' (the number of distinct genotypes present in an isolate).

We have tried to understand whether there are geographical and temporal variations and what the parameters influence allelic distribution and complexity, in particular age, innate susceptibility and immune responses.

Let me now describe the main findings. I hope the audience will forgive me if I take examples from our own work. I use these because of convenience, but let me say that we all find the same things provided we compare what is comparable. There are a few discrepancies in the technical details used, but overall the findings in one holoendemic area are indeed observed in another one, and findings in different mesoendemic areas are extremely consistent.

Population diversity

Most data I will show today concerns a PCR analysis of field isolates using the most popular genetic markers for assessing polymorphism, namely the gene coding for the merozoïte surface proteins, msp 1 and msp2. It shows a very large allelic polymorphism, allowing easy discrimination of isolates based on the polymorphism of these 2 loci. These polymorphisms "flag" each isolate and provide a sort of surrogate estimate of the extent of parasite diversity within the population.

We have done an analysis of parasite diversity in Dielmo and Ndiop, two Senegalese villages located 5 km apart, and in Dakar (Figure 2). The latter has urban malaria in a hypoendemic region, with people being infected elsewhere in Senegal when they visit their parents. We have also done studies in Madagascar with Ronan Jambou, and in French Guyana with Frédéric Ariey on the other side of the Atlantic Ocean.

Figure 2. The villages of Dielmo and Ndiop in Senegal

Allele numeration

It is clear from the results in Table 1 that there are a very large number of alleles in Dielmo, Ndiop and in the isolates collected in Dakar. In contrast, in French Guyana where there is hypoendemic malaria with low transmission and low incidence, parasite diversity is much, much lower. French Guyana is a very interesting place in terms of population genetics.

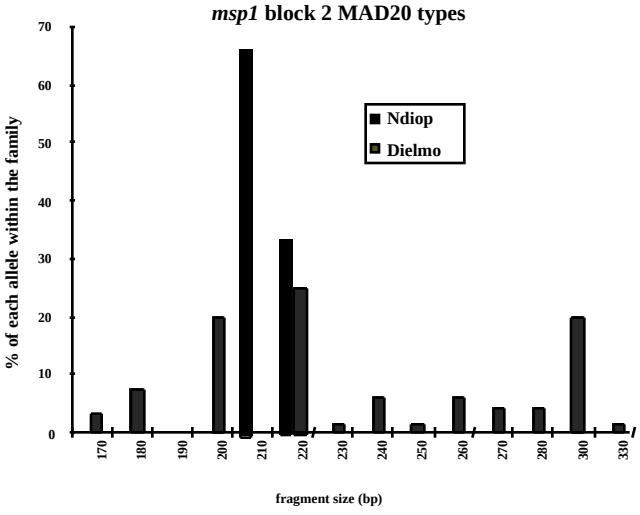
Table 1. Population diversity: number of *msp1* & *msp2* alleles detected in cross-sectional surveys

	Ndiop	Dielmo	Dakar	French Guyana
Number of isolates	125	144	86	125
Msp 1 bl2	13	33	19	4
Msp 2	27	47	31	2

Table 1 shows the number of distinct *msp 1* and *msp 2* alleles, identified by size polymorphism within each allelic family. This is a minimal estimate, because alleles with identical size may have point mutations that remain undetected by this approach.

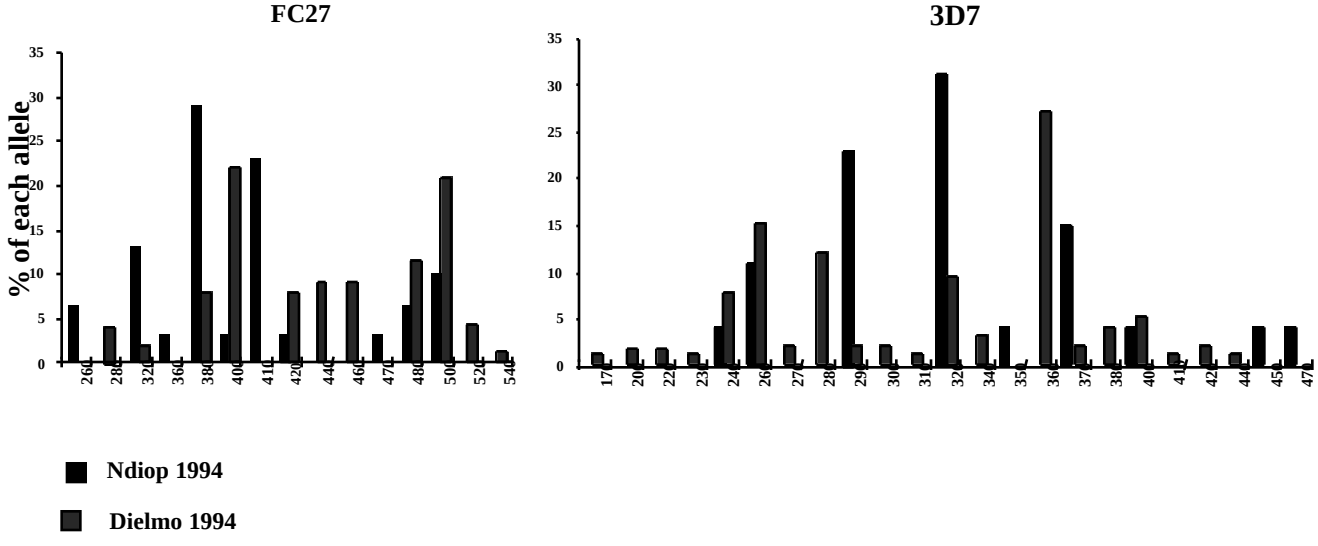
So the first message is that parasite diversity is large, but not everywhere, depending upon the endemicity. There is no linear relationship with the transmission level, but clearly the most diverse population is Dielmo, where transmission is highest.

Figure 3. Distinct individual *msp1* allele distribution in Dielmo and Ndiop, October 1994



Is there geographical variation ?

For us the answer is yes. We have compared the alleles present in Dielmo and Ndiop (approximately 40% of the inhabitants were sampled) in a cross sectional survey conducted in parallel in both villages in October 1994 (Figure 3). This clearly shows major differences in allele distribution. Here is the distribution in both villages of individual *msp 1* block 2 alleles of the Mad20 family. What you see is that the dominant alleles in Ndiop are absent from Dielmo and vice-versa. The same is true for the individual msp2 alleles of both sub-families, the major alleles in one place are minor or virtually undetected 5 km apart (Figures 4 & 5).

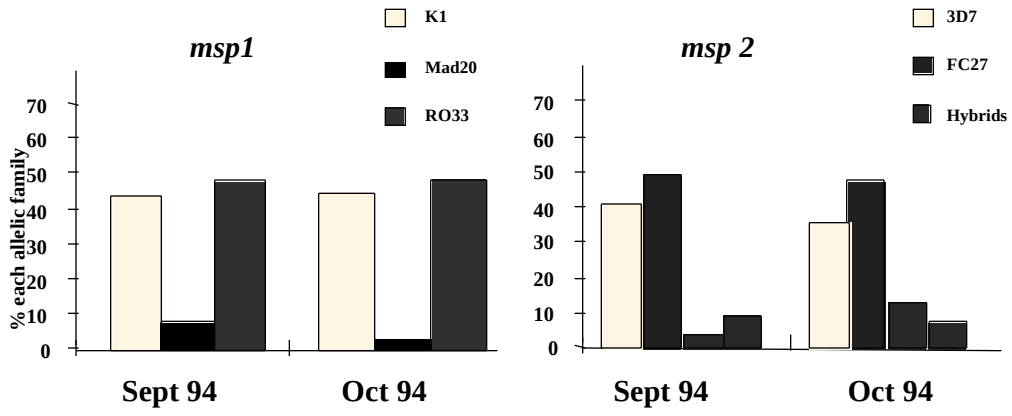


Figures 4 & 5. Distinct individual *msp2* allele distribution in Dielmo & Ndiop, October 1994

Is there variation with time in one place?

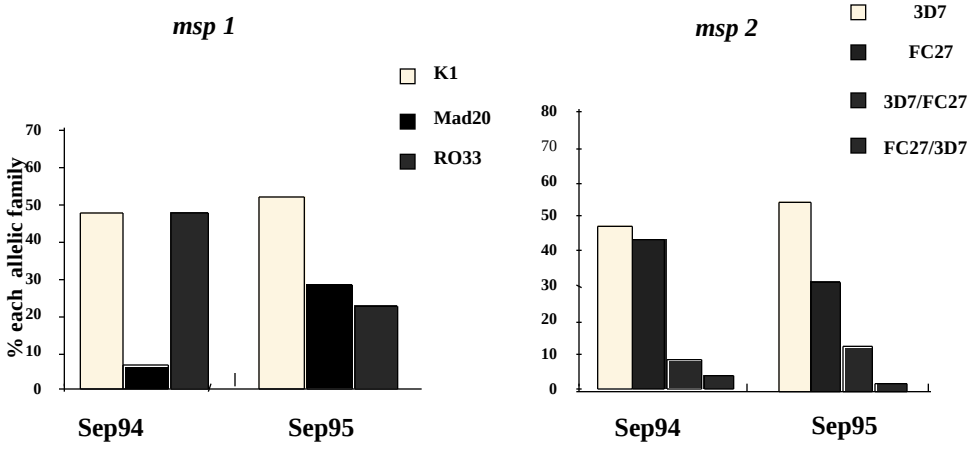
We conducted a series of cross-sectional surveys in Ndiop over a one year period. We first compared two surveys conducted 1 month apart during the 1994 rainy season, namely at a time where parasites are actively transmitted from one person to the next. This showed that allelic distribution in September and October was similar (Figure 6 & 7), reflecting active circulation of genotypes within the village (if one genotype identified in a person in September is no longer in that person in October, it will be found in another person).

Figures 6 & 7 Ndiop: Stable *msp1* & *msp2* allelic family distribution during the rainy season



We also conducted a series of surveys during the following dry season and up to the next transmission season in September 1995. This showed that the parasite population of 1995 was totally different from the parasite population circulating in 1994 (Figures 8 & 9). This was due to substantial variations occurring during persistent chronic carriage in the dry season. I'll describe later what happens during the dry season. So there is substantial year to year variation, at least in this place.

Figures 8 & 9. Ndiop: year to year variation of msp 1 and msp 2 allelic family distribution



In summary, the message is that field parasite populations are very polymorphic and there is extensive allelic polymorphism. Our own analysis of *var* repertoires has so far shown that they are very diverse and this is what the professionals of *var* say too. We have found, and others have also, substantial geographical micro-heterogeneity, as well as temporal variation in allele frequency.

What are the consequences of these findings for vaccination ?

We need to consider local diversity of vaccine candidates in relation to two particular issues:

1. We need to know **more** about diversity, which in practice means sequencing of a very large number of alleles from representative samples of the local population. The big difficulty here is what the word “representative” means and what the word "local" means: does it mean Dielmo or Ndiop? A specific geographical zone? Senegal? West Africa? We need to know much more about what a “population” is for these parasites.
2. The second thing is that we need to understand the **consequences** of such diversity for the immune system. This is a large undertaking and the picture indeed may be quite different for vaccine-induced immunity and for naturally acquired immunity. But we have to study both.

I have unfortunately no time to talk about this. Adrian Hill’s group in Oxford has investigated this aspect for T-cell epitopes, in particular CTL epitopes of the Circumsporozoite protein in man. The outcome is that the epitope diversity is a source of big trouble to existing and future responses.

We have addressed the issue for blood stages, both for antigenic variation and allelic polymorphism, using experimental infections of *Saimiri* monkeys with identified antigenic variants of one parasite line or with different parasite strains. The message is that we have to worry, but not panic. Variant-specific immunity is relayed by recognition of conserved antigens. What seems to be another piece of cake is when we start inoculating several strains and make multiple infections (which is extremely frequent in endemic areas as we will see shortly).

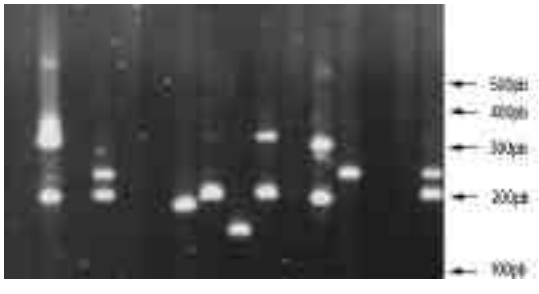
We have also addressed this in the villagers of Dielmo and Ndiop. Hélène Jouin has investigated the allele-specific response against *msp1* block 2 (see poster abstract). Here too the message is that immune responses is specific, but this is not too worrisome as many variant linear epitopes are shared by many alleles, which are built up as mosaics of variable epitopes just like a Lego game with little bricks.

Challenge by heterologous parasites is likely to happen in most endemic areas. In my opinion, protection against heterologous parasite types should be one of the stringent criteria to be used early on in vaccination trials and in preclinical studies.

The last point is obviously that when parasites do come up in vaccines, they should be typed. The gene or the genes coding for the antigen(s) included in the vaccine should be sequenced to look for possible escape mutants.

The second aspect that I will briefly summarise for you relates to infection complexity. Figure 10 illustrates a typical agarose gel where a series of samples has been analysed for *msp1* block 2 polymorphism. As you can see, some samples generate more than one band. As there is only one copy of the gene per genome, the detection of more than one band is synonymous with more than one genotype in the isolate.

Figure 10. Agarose gel analysis of size polymorphism



Many isolates contain more than one genotype The proportion of isolates with multiple genotypes varies in different endemic areas. For instance, in Dielmo where malaria is holoendemic, almost 100 % of the asymptomatic infections contain multiple bands, but only 50% of the isolates in Ndiop where malaria is mesoendemic (Figure 11).

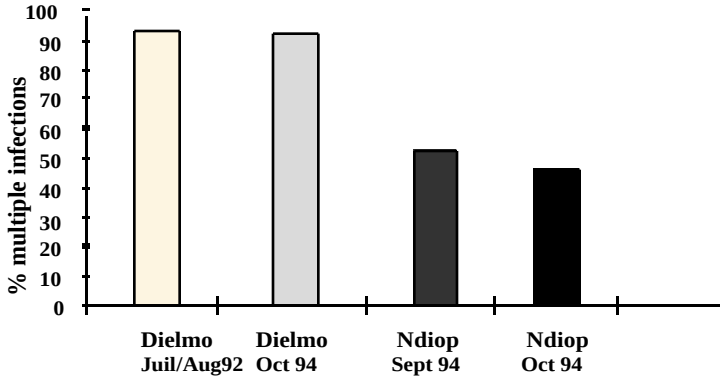


Figure 11. % Multiple infections in asymptomatic Ndiop and Dielmo villagers (transmission season)

Not only is the proportion of isolates with multiple infections different, but also the average number of genotypes per isolate differs. In Dielmo this is about 3.5, whereas in Ndiop this is 1.5. This is true for both surveys conducted in both villages (Figure 12).

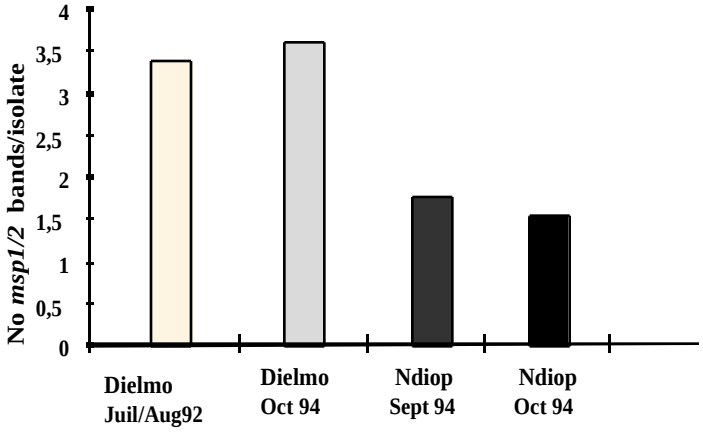


Figure 12. Infection complexity in asymptomatic villagers in Ndiop and Dielmo (transmission season)

Factors influencing complexity

I have no time to go into details on the factors influencing complexity and a special issue of the Transactions has just been published under the auspices of the Swiss Tropical Institute. However, to summarise the key points: complexity is influenced by transmission intensity, parasite density, age in holoendemic but not in mesoendemic areas, and by treatment.

Longitudinal studies

Let me now move to what we have learnt from longitudinal molecular epidemiology studies and the implications of the results for vaccines. Longitudinal studies have provided new insights into the dynamics of infections, on the factors which contribute to the occurrence of clinical attacks and on what it happening during chronic and asymptomatic infections.

In Dielmo, Jean-François Trape and Christophe Rogier have conducted an extremely well-documented longitudinal survey during the 4 months of intense transmission of the 1990 rainy season, with daily monitoring of clinical symptoms and measurement of parasite density 2-3 times a week.

Here is an example of a child who has suffered three clinical successive attacks of malaria within a period of 3 months (Figure 13). The parasite density is recorded above and the body temperature below. Each rapid steep increase of parasite density is associated with clinical symptoms, which are then treated.

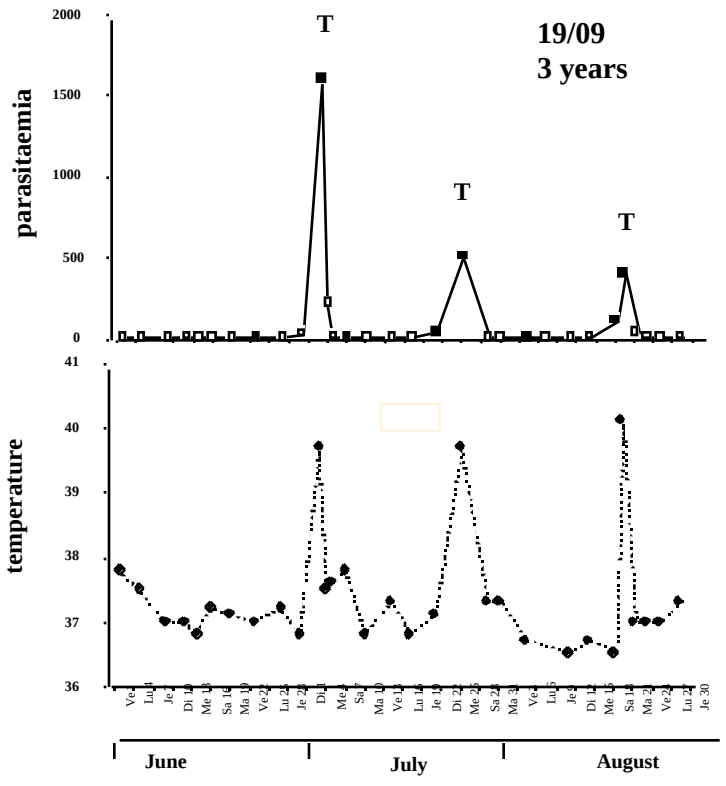


Figure 13. Childs successive clinical attacks within three months.

We genotyped parasites collected from the children during each clinical episode and systematically every second week. What came out was a very clear cut conclusion. The parasites collected were different for each episode. The DNA collected systematically and that collected four days later during the episode were genetically identical, indicating that those parasites that were present at low density on one day multiplied to high density and provoked the episode.

The conclusion that parasites collected during successive clinical episodes experienced by children are genetically different was valid for all cases, except when there was a recrudescence due to incomplete treatment. Such clear cut infections are not always the case. There were other cases where the dynamics of infections were more complex, with alternating symptomatic and asymptomatic phases. However, the conclusion that I just stated remains true: for each clinical episode which required treatment, parasites were genetically different, and clinical episodes were caused by parasites that multiply very quickly.

However, not all -new infections end up in a clinical episode. You see here that the parasites collected from this child do not reach a very high density and are controlled. The parasites differ from those collected 6 days later during the second episode.

To summarise, what we have learnt is that clinical episodes are associated with rapid multiplication of recently inoculated parasites which reach high density (above a pyrogenic threshold, which is dependent upon endemicity). Clearly the parasites collected during successive clinical episodes experienced by these children over this four month period were genetically different (Figure 14). The other noticeable observation is that children control multiplication of some genotypes (and then the infection is asymptomatic), but not of others which grow fast, passed the threshold density and cause a clinical episode.

In terms of vaccination, this indicates that **control of the parasite multiplication rate** is an essential component of protection against clinical malaria and sterile immunity may not be a pre-requisite. It looks as if to reduce the multiplication rate is enough to slow down the pace of infections and provide time for the immune response to become effective. All trials that have been done in animal models have looked for a 'yes' or 'no' reply, and have aimed at inducing a golden, sterile immunity. Reducing growth rates from steep curves to flatter ones may be sufficient to prevent symptoms and to leave the time for protective responses to take over and do their job.

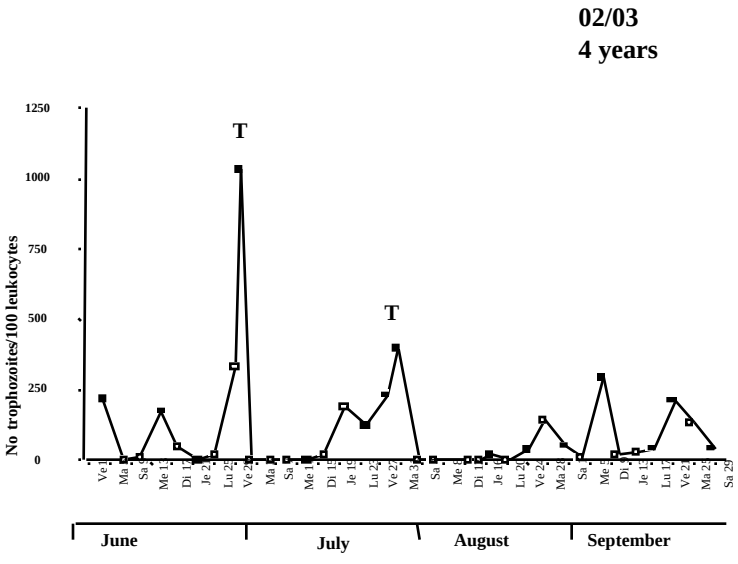


Figure 14. Clinical episodes over four months

In the last part, I want to briefly address the issue of infection dynamics in asymptomatic subjects. I think there is confusion here and we need to distinguish between occurrences in different transmission conditions. The situation differs in people who are frequently superinfected, during heavy transmission periods in holoendemic areas, and in those with chronic infections in the dry season, when there are no mosquitos around, and in mesoendemic areas, where people receive ten or fifty times less infections than in holoendemic areas. Findings in holoendemic areas cannot be extrapolated to other places.

In brief, the conclusions for infection dynamics in asymptomatic subjects are as follows. When parasites are actively transmitted and novel inoculations occur at high frequency, we observe a rapid turn-over in the peripheral circulation. This has been so far observed only in holoendemic areas.

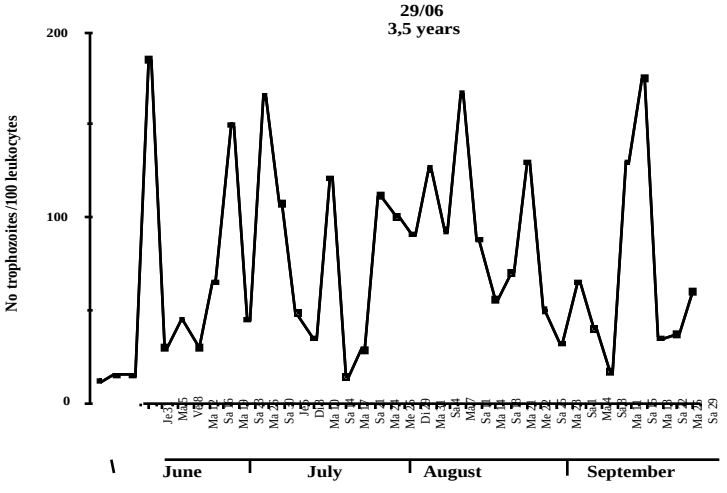


Figure 15. Parasite record of untreated girl from Dielmo

When there is no transmission, during the dry season, then the situation is very different. Prolonged carriage of single clone infections occurs, or alternatively, if the dry season starts with a multiple clone infection, then we observe fluctuations in the various parasite types.

Figure 15 is the parasite records of a 3,5 year old girl from Dielmo collected over 2 months during the same 1990 rainy season. She remained untreated throughout this period.

We analysed five isolates collected from this child. Each one generated a distinct pattern, indicating a rapid turnover of parasites in the periphery (Figure 16). These samplings were done approximately every second week (day 1, day 16).

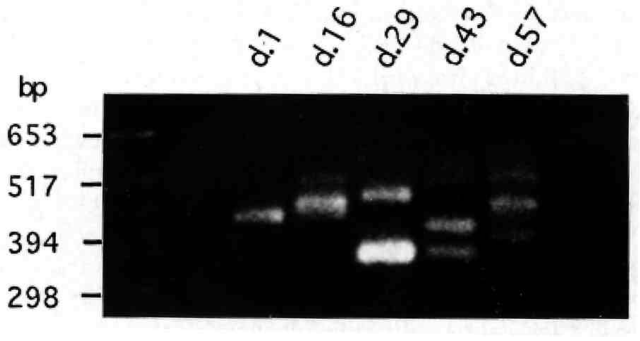


Figure 16. Base pairs at two weekly intervals

We then studied more precisely the parasite dynamics and collected blood on even or uneven days, in order to investigate parasites that were sequestered the day before. Turnover of parasites was again observed, with parasites detected on days 1 - 5 being "replaced" by another population (Figure 17).

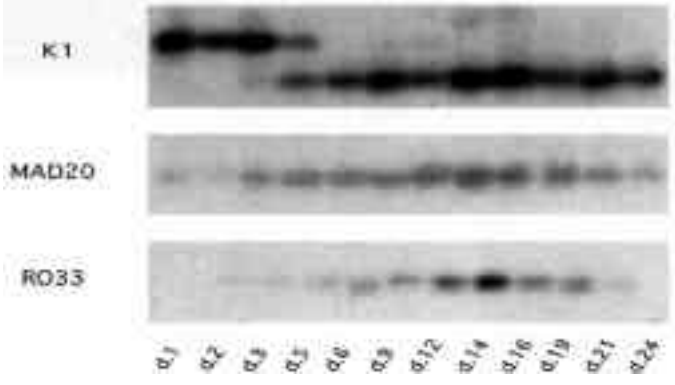


Figure 17. Parasite dynamics over odd and even days.

Similar data have been observed in a holoendemic village of Tanzania by Anna Farnert, Georges Snounou and Anders Bjorkman. There are daily fluctuations of the genotypes circulating in the peripheral blood.

No doubt when transmission is intense, infections are complex and there is a rapid turnover of the population in the periphery. Dominant parasites change frequently. We have calculated that a specific genotype was observed for about 2 - 3 weeks.

The opposite is observed in places where transmission is interrupted and people carry single clone infections. Pierre Daubersies has studied chronic infections in Pikine, a locality close to Dakar where malaria is hypoendemic. The same clone was observed throughout the survey (5 weeks), indicating stable carriage.

As I mentioned before, we have recently conducted an analysis of chronic carriage at the village level during the dry season in Ndiop. Figure 18 is data from Didier Fontenille and his colleagues showing the entomological inoculation rate, which has been monitored monthly throughout this three year period.

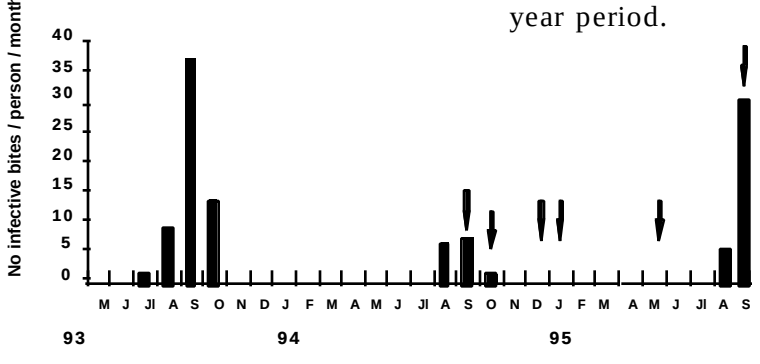


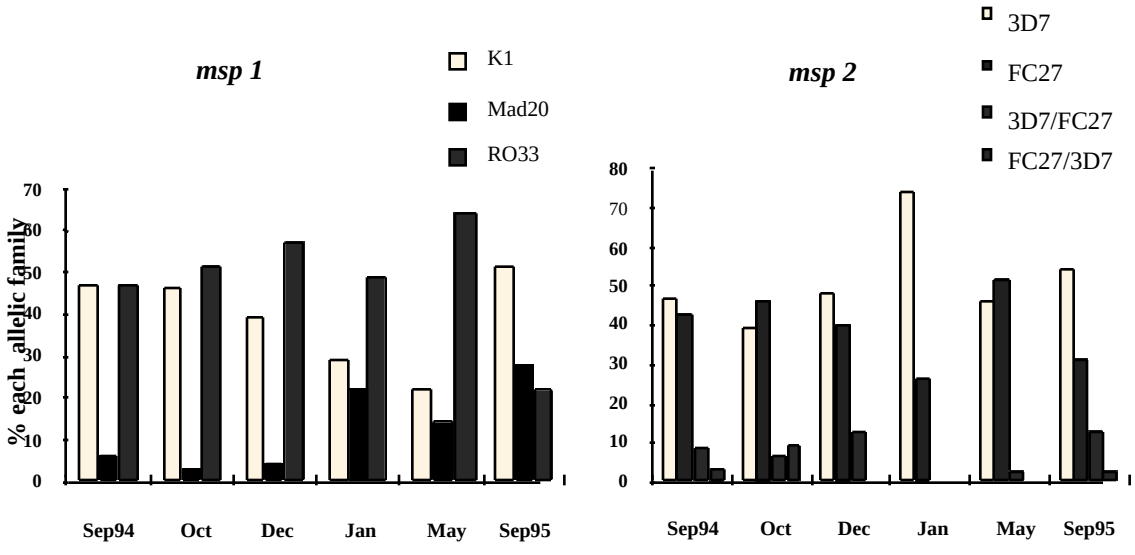
Figure 18. Entomological inoculation rate in Ndiop

We have observed 2 things. Firstly, there was a

considerable temporal variation of the parasite population during the dry season when no mosquitos were captured. This resulted in the September 95 population being very different from the September 94 one, as I mentioned earlier (Figure 19). Only one out of 46 individuals studied had the same single band genotype throughout.

All the others had a genotypic profiles that differed from those detected in the earlier surveys. This is not due to novel inoculations. We think that this reflects a major variation of the dominant population infecting a person upon prolonged, chronic carriage: parasites that were barely or not detected at the onset of transmission take over progressively to become the dominant population after a few months.
Similar fluctuations have been observed previously during the dry season in Sudan in two different villages. It therefore looks as if there are major changes in the population as a whole during chronic carriage where serious selective forces are obviously opposing the parasite.

Figure 19. Ndiop: temporal variation in msp1 and msp2 allelic family distribution



The second very interesting and unexpected finding was that after seven months of undetected transmission, parasite prevalence significantly drops in younger children. Figure 20 shows the prevalence in children under 7 years, in 7-14 year-olds and in those above 15 years. The prevalence drops progressively upon prolonged absence of inoculation in the youngest children. This is quite amazing as children are thought to have the least efficient anti-parasite immunity. These of course are untreated villagers.

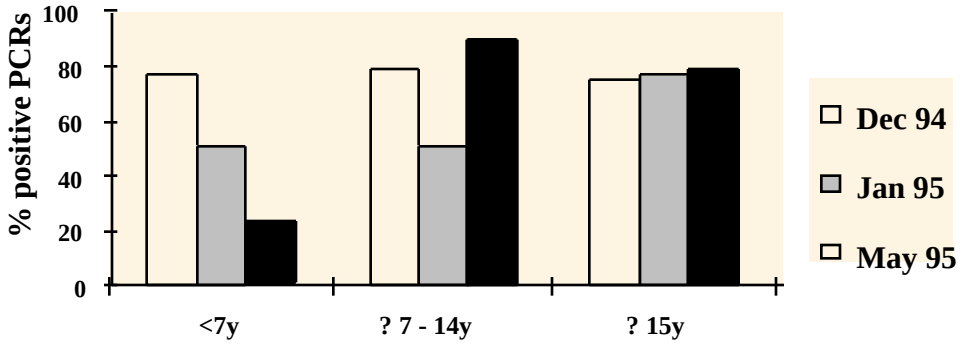


Figure 20*. P. falciparum* prevalence by age during the dry season in Ndiop

So interesting things happen during the dry season:

- There is a specific reduction of prevalence in younger children. Whether this reflects total elimination or simply a substantial reduction in density in younger children is unclear.
- There are also major changes in allele distribution during the dry season.

This ends up with an interesting picture which makes sense: young children at the onset of the next transmission are predicted to have a reduced concomitant immunity. They have an increased susceptibility to infections due to decreased clinical immunity and to the fact that their anti-parasite immunity is limited. If on top of that the face of the parasites has changed during the dry season, then this further increases their risk of a clinical episode once they get infected during the next transmission season.

Conclusions

In conclusion we have learnt that :

- Field parasite diversity is large in most places.
- Heterologous challenge is likely to be the rule. This means that the immune system is frequently faced with novel antigen combinations, and even conserved epitopes are exposed to the immune system in novel contexts, because they are associated with variable determinants.
- Mixed infections with multiple clones are very frequent, including in places where transmission is moderate or low, and this is somewhat puzzling.
- Parasite densities and type fluctuate, which means that allele ratios vary with time, presenting difficulties for the immune system.

To finish I wish to stress that what we have also learnt is that many molecular epidemiology parameters, such as turnover of peripheral population, complexity and even extent of diversity, differ with transmission and endemicity. This is yet another illustration of what has been stressed several times in this meeting: malaria is diverse and we must be cautions not to extrapolate too much from one type of endemicity to the other.

BREAKOUT SESSIONS: MALARIA VACCINES AND IMMUNOLOGY

Programme

1. Malaria Vaccines: Basic Research.

Chairs: Dr. Andrew Kitua, Professor Louis Miller.

Dr. Fred Kironde, Dr. Don Krogstad and Dr. Sirima Bienvenu

Panel : Louis Miller, Brian Greenwood, Michael Good, Soren Jepson, Wen Kilama.

Presentations

1. Basic Research - Steve Hoffman (15 minutes).
2. Interspecies conserved proteins of *P. falciparum* as potential vaccine candidates - Fred Kironde (10 minutes).
3. Immunogenicity and in vitro protective efficacy of novel recombinant multistage *Plasmodium falciparum* malaria candidate vaccine - Altaf A. Lal (10 minutes).
4. Natural immunity against Pfs 48/45 a gametocyte antigen vaccine candidate - Mike van der Kolke.
5. Role of immunoglobulins as binding molecules in rosetting of *P. falciparum* - Geoffrey Pasvol (10 minutes).
6. Rifins: A new family of *P. falciparum* proteins that are expressed on the surface of infected erythrocytes - Alexander J. Rowe (10 minutes).

Discussion and recommendations on lessons learnt and concrete plans for future.

2. Malaria Vaccines and Immunology

Chairs: Professor Marcel Tanner and Colonel Ripley Ballou

Rapporteurs: Dr. Ibrahim Elhassan and Dr. Francine Ntoumi

Presentations

1. RTS.S Overview (Introduction). - Ripley Ballou (5 minutes).
2. Schedule optimisation of the *P. falciparum* circumsporozoite hepatitis B-surphase antigen subunit vaccine RTS.S/SABS2. - Kent Kester (10 minutes).
3. Safety, immunogenicity and field efficacy studies of a *P. falciparum* malaria pre-erythrocytic vaccine. - Kalifa Bojang (10 minutes).
4. Safety and immunogenicity of the lyophylised RTS-S/SBAS2 malaria vaccine in a malaria- experienced adult population of West Kenya. - Jose A. Stout (10 minutes).
5. SPf66 - 1998 Tanzania Results. - Andrew Kitua, Pedro Alonso and Marcel Tanner (10 minutes).
6. SPf66 - Lessons learnt and future perspectives. - Pedro Alonso (10 minutes).
7. Malaria and concomitant measles infection. - Vivienne Tchinda.

Discussion (1 hour).

3. Malaria Vaccine Field Trials and Capacity Building

Chairs: Professor Brian Greenwood and. Dr. Pedro Alonso

Rapporteurs: Dr. Ritha Njau and Dr. Fulvio Esposito

Presentations (10 mins each)

1. Allelic diversity at the merozoite surface protein –1 and –2 locus of *P. falciparum* in isolates collected from Cameroonian children - Francine Ntoumi.
2. Effect of blood group, sickle cell trait and G6PD deficiency on mixed and sub-patent malaria - Olusegun Ademowo.
3. Functional analysis of *P. falciparum* EBA-175 Immunological population genetic and in vitro approaches - Daniel Okenu.
4. Identification of protective T-Cell epitopes in *P. yoelii* infection - Morris Makobongo.
5. Comparative IgG1/IgG3 antibody responses over time to MSP119 in two different areas of *P. falciparum* transmission - Olivier Garraud
6. Immunoepidemiological studies of humoral immune responses to *Plasmodium falciparum* antigens in an area characterised by seasonal and unstable malaria transmission in Sudan - Ibrahim Elhassan.
7. IFN-g Responses to infection - Adrian Luty.

Field Trials/Capacity strengthening: short, mid and long-term plans and recommendations.

Summary Report: Malaria Vaccines and Immunology

Introduction

Over 100 years after Ronald Ross 's discovery of the parasitic cause of malaria and its mode of transmission which involves the mosquito vector, malaria is still affecting 40% of the global population and is the most important public health problem of poor countries followed by HIV/AIDS.

Like other diseases, its control requires an interplay of effective strategies for providing cure to the sick and prevent the general population from getting sick. This interplay has been difficult to achieve in malaria because while effective curative drugs have been available for a long period, preventive strategies have not been adequate for most of the tropical poor countries. It has been difficult to stop transmission through vector control methods, a strategy highly advocated in the 50s and early 60s, because of the vastness of breeding sites, and the poverty has played an important role and is a major stumbling block.

The development of vector resistance to insecticides (one of the current arsenals in vector control) and parasite resistance to the existing cheap and affordable drugs like chloroquine makes malaria control a serious and difficult issue.

The development of an effective and affordable vaccine is therefore a matter of urgency in order to improve upon the current arsenals for malaria control.

Tremendous work has already been done in this area over the last two decades following the demonstration that attenuated irradiated sporozoites provides full protection to vaccinated individuals. Many vaccine candidates have been Identified although so far only a few have reached the stage of testing in humans.

The major challenges in the development of a malaria vaccine include

- Poor funding allocation to malaria vaccine development efforts. Malaria is a poor-country disease and the drug industry has had little interest in this field.
- The complexity of the parasite and its life cycle. It is generally accepted that the ideal vaccine should be multigenic and multistage. How to identify and combine the most potent antigens is a major challenge.
- The huge genome of the parasite. The P. falciparum genome project is expected to provide the major support in this area facilitating the identification of potent antigens and possible combinations.
- Difficulties to culture the parasite and produce in mass the attenuated sporozoite vaccines. Efforts in synthesizing the relevant peptides and the recombinant vaccine strategies are aimed at solving this problem.
- Active involvement of the countries with the problem in developing the vaccines and undertaking field trials.

The Multilateral Initiative on Malaria (MIM) and the recently Roll Back Malaria movement are strong indications that the world once again has recognised the important global problem of malaria and that only joint efforts can make a difference in this area. Both initiatives have and are strong advocates for the allocation of adequate funds for malaria control efforts and have in common the goal of strengthening the capacities of the poor affected countries in solving the problem. Strengthening links between northern institutions

and laboratories with advance knowledge and technology in vaccine development and southern institutions has been encouraged.

The status of malaria vaccine development, the challenges ahead and strategies to overcome them were discussed during the malaria vaccine sessions. Keynote presentations will be presented elsewhere [1, 2, 3].

1. Malaria Vaccines: Basic Research

Current research activities in this field of vaccine development include the search for new and potential molecules or genetic components belonging to the *P. falciparum* stages which can be developed as components of a new vaccines. It was reported that a new family of riffin genes that are specific to later - ring and trophozoite stages of *P. falciparum* have been identified (Rowe A. *et al*). Metabolic label experiments showed that indeed they originated from the parasite while surface labelling and trypsinazation techniques demonstrated that they are located on the surface of the parasite cell. Although their significance is not known, this family of genes is highly repeated in the genome and has potentials for vaccine development.

Promising results of a new vaccine candidate, a yiest-expressed recombinant vaccine RTS,S which contains the repeat sequences of Cercumsporozoite Surface Protein, a T-epitope and S antigen of Hepatis B were presented (Ballou R. *et al*). The vaccine formulation has been shown to be safe, immunogenic and was able to present malaria in 6/7 naive volunteers challenged with homologous parasite strains. This is a very promising vaccine candidate and currently field studies are under preparation in the Gambia and Kenya.

Another novel recombinat multistage *Plasmodium falciparum* candidate vaccine formulation termed CDC/NIIMALVAC-1 has been developed (Altaf A.Lal et al). The product is expressed in Baculovirus from a synthetic gene representing epitopes from nine *Plasmodium falciparum* antigens. Immunization in mice and rabbits elicited protective antibody and cellular immune responses to the vaccine and partner pepticle.

In the area of transmission blocking vaccines, the development of cellular immunity against Pfs 48/45 and the longevity of anti-Pfs 48/45 antibody reactivity was described (Van der Kolke et al.). Cellular and antibody immunity against Pfs 48/45 were analysed in Yaounde volunteers representing uninfected, and carrier of asexual and gametocyte stages of *Plasmodium falciparum*. *O*nly a minority of individuals exposed to gametocyte showed Pfs 48/45 dependent lymphocytes proliferation. Gametocyte careers and non-careers produced anti-Pfs 48/45 antibodies.

Rosetting of P.falciparum infected red blood cells is a phenomenon which is linked with the sequestration of P.falciparum infected red blood cells. The question is what serum components are involved in rosetting? Dr Paslvol described the role of immunoglobin in the rosetting of *Plasmodium falciparum* infected erythrocytes. In the search to assess the requirement of IgG and IgM in rosetting, an assay system was used where when schizonts were stripped of serum components and incubated in a serum free medium(Albumax I) rosetting did not occur, but was restored by additng serum to this media. It was shown that IgG depletion had no effect on the rosetting rate while IgM-depleted serum supported rosetting to only 50% of the controls and addition of purified IgM fraction increased the rosetting rate to

80% and rosette size. It was suggested that IgM is not singly involved in rosetting but throgh a complex system that may require other serum components.

Novel approaches for identifying new vaccine candidates are needed and in this respect three improved approaches for the discovery of new targets of vaccines and drugs were discussed (Kironde F, et al.). The method involves the production of anti-P.yoelii serum that can be used to probe for new interspecies conserved antigens of *Plasmodium falciparum* . In this study, by co-probing P.falciparum expression libraries with mouse anti-P.yoelii sera and rabbit anti-IMP serum, putative aepical merozoite antigen 70Kda (pf70) , an immunogenic antigen shared between P.falciparum and P.yoelii was identified and is thought to be a transmembrane molecule. A third antiserum probe specific to apical organelles of *Plasmodium falciparum* was also described.

[1,2,3] Keynote presentations by Dr. O. Puijalon, Dr. P. Hoffman and Prof. W. Kilama

2: Malaria Vaccines and Immunology

The past decade has witnessed remarkable progress in the field of malaria vaccine development. Two candidate malaria vaccines in particular (RTS,S and SPf66) have undergone intensive clinical development, including clinical trials in Africa. Our Progress in the developments of the two vaccines candidates is presented below.

SmithKline Beecham's recombinant RTS,S malaria vaccine has been under development since the late 1980s. The program has been driven by the need to establish a robust industrial manufacturing process for recombinant antigen and to identify a formulation that would induce intense but appropriate protective immune responses. The objective of the RTS,S vaccine program is to develop a vaccine that will protect children against infection with the parasite. The near term strategy is to focus on preerythrocytic antigens (CS and TRAP) and induce antibody and T cell responses that will stop the parasite before it completes liver stage development and thereby prevent blood stage infections or significantly reduce the inoculum of merozoites into the blood stream. A long term objective is to add an asexual stage antigen, such as MSP-1, to attack any few merozoites that might escape from the liver and prevent the establishment of clinically significant parasitemia. The RTS,S vaccine consists of a yeast-expressed fusion protein containing the repeat (R) region of the CS, plus its C terminal flanking region containing T-cell epitopes (T). RT is fused to the hepatitis B surface antigen (S). This RTS fusion protein is coexpressed with unfused S antigen, and spontaneously yields immunogenic particles referred to as RTS,S. A series of clinical trials revealed that a strong adjuvant was required for protection against experimental sporozoite challenge. This adjuvant is referred to as SBAS2 and is an oil-in-water emulsion containing QS21 and MPL as immunostimulants. The initial studies were performed with a liquid version of the vaccine, but it soon recognized that accelerated degradation was occurring in some clinical lots. This led to a reformulation of the antigen as a lyophilized product to which the liquid SBAS2 is added prior to injection. Results of a recent Phase I/IIa trial comparing the safety, immunogenicity and efficacy of lyophilized RTS,S compared to liquid RTS,S were presented (Kester K. *et al*). These studies confirm the safety and immunogenicity of the new formulation and reveal comparable efficacy after a two dose regimen (Å50%). Interim results of a Phase IIb field trial of liquid RTS,S in adults living in a rural Gambia community with seasonal malaria was further reported (Bojang *et al*). No efficacy data are yet available. Dr. J. Stoute reported interim data from a Phase I clinical trial of the newly lyophilized formulation in adult Kenyans living in an area of intense year-round transmission near Kisumu was also described (Stoute J. et al.). The vaccine was safe and immunogenic after first dose. Field site development in anticipation of a Phase IIb trial of the new RTS,S/TRAP vaccine later this year is in preparation. This combination vaccine has been found to be safe and immunogenic in Belgian adults, and will undergo Phase I/IIa challenge studies in the US soon.

SPf66 in an alum-adjuvanted sysnthetic peptide polymer vaccine directed against the asexual stage of the parasite that has been studied extensively over the past nine years. The vaccine was developed empirically in an academic setting and has never had the benefit of significant industrial involvement. Consequently, the product underwent limited process development before clinical trials were initiated, and this has led to many questions concerning product characterization and lot-to-lot consistency that have complicated the interpretation of the conflicting results obtained from several large field trials. Drs. M. Tanner, D. Schellenberg, P. Alonso and A. Kitua revealed publicly for the first time, the results of the most recent field

trial to have been completed with SPf66. This was a large RPCDB study involving more than 1000 infants followed at the Ifakara field site in Tanzania. The study was a follow-on study to an earlier trial carried out in Ifakara in children under 5 that indicated that the vaccine efficacy was Å31% (C1 0-52). In the new trial, the vaccine was administered to infants in a regimen that was integrated into the local EPI program. Infants were followed closely for the development of clinical malaria. The vaccine was safe and well tolerated, but no protection was observed. It was concluded that the presentation with a recommendation that no further clinical studies of SPf66 in its current formulation in Africa were indicated, but urged that the substantial investment in field site development in Ifakara be sustained.

This session was concluded by an interesting study conducted in Cameroon which investigated the relationship between measles and malaria infection and diseases (Tchinda et al). Children presenting with measles were studied by PCR to detect coinfection with malaria, and outcomes were compared. The data indicated that concomitant infection nearly doubled the mortality rate from measles in this population. If confirmed and extended to other diseases, they suggest that the beneficial effects of a malaria vaccine might extend to other important childhood illness.

Implications for Control Programs

Remarkable progress has been made and exciting candidates are being developed. However, resources are very limiting, and a licensed vaccine is at least 10 years away. Therefore, existing control programs must be strengthened and sustained. Communication between the vaccine community and control programms is essential.

Strengthening Constructive Links

The experiences in Tanzania, The Gambia and Kenya emphasize the fact that field sites for vaccine trials require sustained support, and once established, these links require continued investment. The malaria community must capitalize on capacities already developed find new ways of sharing and extending their experience and resources. We must develop a greater understanding of the epidemiology of the disease in new and existing field sites, and a recognition of the needs and expectations of the study community.

Research Capacity Needs

The vaccine community must develop the capacity to conduct more trials. Several difficult questions were raised: Are there new ways of approaching vaccine trials that would make them faster, cheaper, simpler? The notion that a malaria vaccine would need to be given with EPI may not be based on sound epidemiological data. If needed, how would one apply a vaccine outside EPI?

Resources are limited - when should development of a particular vaccine candidate stop? Can surrogate markers or correlates of immunity be used to make this process more rational?

3. Malaria Vaccine Field Trials and Capacity Building

Field trials and related activities were presented as a demonstration of additional capacities being built in the field of Malaria Vaccines.

Allelic diversity is an area which has attracted research attention in attempting to pin out the determinants of disease presentation (severe or mild). Allelic diversity at MSP-1 and 2 locus

of *P.falciparum* from a total of 73 children from Dienga, Gabon and Pooma, Cameroon were studied (Ntoumi F. et al.). Out of these 19 were symptomatic and 54 non symptomatic parasite carriers. It was shown that there was no difference in the distribution of alleles between the two groups. However carriage of allele a and b was highly anociated with the disease (a = FC 27/390 bp, b = FC 27/610 bp). There was large polymorphism with MSP-1 and MSP-2 in both places.

The question of cross sectional vs longitudinal studies in children for further exploration of this issue was raised and it was recommended that obtaining isolates from a cohort followed up over time could give more useful information.

A longitudinal study on the function of *P. falciparum* EBA-175 in terms of Immunology, population genetics and in vitro approaches was presented (Okenu et al). It involved 284 Gambian children aged from 2-9 years. Sera was collected in May (prior to transmission season) while clinical and parasitological follow-up was continued till October in order to capture malaria outcome.

The results showed that:
1. There was a strong correlation between serum reactivity of Gambian donors to the Fseg & Cseg (r = 0.85).
2. Ab prevalence to Fseg, Cseg & region III-V were age-dependent, as expected, reaching peak at adolescence.
3. Logistic regression analysis against Ab to Fseg, Cseg & region III-V did not yield evidence for protection against clinical malaria.

On the identification of protective T-cell epitopes in *P.yoelii* infection, Dr. Morris Makobango presented an interesting study which used experiments with B-cell knockout (KO) mice.

Results showed that there was:
1 Significant delayed onset of parasitaemia in immunized B-cell KO mice.
2. B-cell KO mice that received P. yoelii specific T-cells showed very low levels parasitamia (<10%).
3. (7-18K Da) soluble proteins are apparently responsible for the T-cell mediated protection.

In comparing IgG1/IgG3 Ab responses to MSP-$1_{19,}$ a study which examined the frequency, intensity and evolution over time of IgG1/IgG3 antibodies before and after the highest transmission period in groups of clinically immune adults from Dielmo and Ndiop, Senegal was presented (Garraund O. et al.). The study involved 60 individuals from each locality.

Results showed that:
1. Frequency and intensity of IgG1/IgG3 responses were significantly higher in Ndiop than in Dielmo, reciprocally to the degree of parasite exposure.
2. The data suggest that anti-MSP-1, IgG1 and IgG3 are differently, regulated after the HTP unlike before this period in clinically immune adults.
3. The importance of the dynamics in the production and utilization of IgG1 vs IgG3 in the maintenance of acquired immunity to MSP-1.

A study from Daraweesh, Sudan to determine humoral immune responses to Pf MSP-1, Pf155/RESA, CSP and GLURP in plasma sample (Elhassan I et al) showed that:

1. Antibody levels to both RESA and GLURP are increased markedly between the beginning and the end of the transmission season.
2. High titers were observed in acute plasma samples.
3. Responses to the C terminal of MSP-1 Ag occured in the majority of the acutely infected individuals.

Finally the results of a study cohort of 100 Gabonese children with either severe mild malaria (matched) was presented (Luty ATF et al). The study aim was to explore the association of IFN.R responses with resistance to reinfection with P. falciparum in young African children.

The results showed:

1. Those with severe malaria had significant shorter delay to first reinfection as well as significant higher rate of reinfections.
2. Time to first reinfection: mild = 43 weeks, severe = 29 weeks.
3. Delay to first reinfection was significant longer in individuals whose cells produced IFN-R in response to peptides derived from LSA-1 or from MSA-2 = but this association was found in the group with mild disease.

Group discussions and recommendations:

Partnership and Capacity Building

It was recognised that there were only a few centres in Africa capable of using available results of Northern Laboratories in all field in the process of developing field control tools. Hence

1. Need to strengthen existing Labs/Institutions in Africa to undertake more work on Vector Biology, Molecular Epidemiology, Pathogenesis, Immunology and Molecular Parasitology.
2. Establish and maintain capacities for *Plasmodium falciparum* culture in order to test new drugs. Regional Labs with this capacity could act as supplies of *Plasmodium falciparum* culture materials to other labs as need arises.
3. Establish at least on regional basis centre/labs capable of conducting vaccine challenge trials establishing protection in semi-vaccine immune populations.
4. Increase the number of sites capable on conducting Phase I-III Vaccine trials.
5. The donor community must be sensitized and advocacy for malaria control which required an efficacious vaccine/s should be maintained. Malaria elimination will make the world a lot better and healthier place to live in.

Research Priorities

Short Term:

1. Complete development of new candidates (RTS,S & others) should be accelerated.
2. Consideration of the impact of parasite diversity on vaccine design is essential.
3. Identification of better endpoints and surrogate markers to make trials easier, faster, less expensive should also be accelerated.
4. There is need for in-depth study for vaccine candidates in field conditions.
5. Suitable models to predict what happens on humans are required.
6. Available genotype data should be analysed in order to see what they present in the large scale.

7. On the choice between polymrphic versus conserved antigens for vaccines, it was suggested that conserved genes are preferable.

Medium Term:

1. Identification of an effective vaccine remains the goal
2. Pivotal Phase III trials in target populations must be designed and executed to high standards
3. There is need for longitudinal studies to determine the turnover rates for some genotypes and their significance in relation to clinical presentation.
4. In depth studies on Var-genes and the role of gametolyte carriers are needed.
5. There is need to monitor the response of MUST DO 15 and extend the current findings as well as sorting out the components of MUST DO 5.

Long Term:

1. Consider how best to implement a vaccine into control programs
2. Evaluate the impact of vaccination in early life.

Link Between Research and Control

1. As yet no vaccine is available for control and therefore the message to the control community is that while waiting for the vaccine, utilization of existing tools in synergistic manner can make a difference.

2. Insecticide impregnated mosquito nets have been shown to reduce overall mortality of children by 35% and their continued use together with improvement in early diagnosis and proper case management will save many lives.

3. Communities must be encouraged and helped by all means to protect themselves from mosquito bites, clean the environment and reduce mosquito breeding sites and use prompt diagnosis and treatment as part of their culture for health living.

4. For effective malaria control, efforts must be directed at the development of an efficacious vaccine within the next ten years.

5. For Africa, the best choice is a vaccine that would reduce mortality. An ideal vaccine would be multigenic and multistage and efforts to produce such a vaccine, which would be able to counteract all stages of the parasite are being made.

VECTOR BIOLOGY AND CONTROL

Plenary Presentations

Malaria Vector Population Studies: Potential Contribution for Selective Control Measures

Yeya T. Toure´

Vector Control : Insecticide Impregnated Bednets for Africa– Implementation, Prospects and Challenges for malaria control

Halima A. Mwenesi

Breakout sessions

Programme

1. Insecticide Treated Bednets
2. Vector Biology and Control
3. Vector Biology and Control - ITNs and Selective Vector Control

PLENARY PRESENTATIONS

Malaria Vector Population Studies: Potential Contribution for Selective Control Measures

Yeya T. Toure´, Malaria Research and Training Centre, Bamako, Mali

Introduction

Following the Ministerial Conference on Malaria in 1992 in Amstersdam and the WHO's strategic plan for malaria control, the goal of malaria control is to prevent mortality, reduce morbidity and social and economic losses, through the progressive improvement and strengthening of local and national capabilities.

The four basic technical elements of the strategy are:

1. To provide early diagnosis and prompt treatment.
2. To plan and implement selective and sustainable preventive measures, including vector control.
3. To detect, contain or prevent epidemics.
4. To strengthen local capacities in basic and applied research in order to permit and promote regular assessment of a country's malaria situation in particular the ecological, social and economic determinants of the disease.

The selective vector control strategy aimed at reducing malaria transmission will have to be built upon basic information on vector biology, ecology and genetics. Such studies will help in characterising in different eco-climatic conditions:

- the malaria transmission intensity and dynamics
- the vector behaviour
- the vector susceptibility to *Plasmodium* and insecticides

Vector Biology, Ecology and Genetics

Characterization of malaria transmission intensity and dynamics

The knowledge, under defined conditions, of how much transmission is occurring (intensity: expressed as cumulative number of infective bites for the period of transmission), the length of transmission (duration: seasonal, perennial..), the patterns of transmission (unimodal, bimodal…), the level of stability of the transmission and the factors governing these characteristics (environmental conditions: climatic, socio-economic….) are elements for understanding malaria transmission, and for planning and implementing control measures.

Vector behavior and susceptibility to *Plasmodium* and insecticides

Vector man-biting rate (number of bites received per man per unit time), infection rate (relative proportion of vectors having *Plasmodium* sporozoites in their salivary glands), anthropophilic rate (relative proportion of vectors with human blood), and vector longevity (probability of survival of the vectors, life expectancy and particularly the infective life expectancy) are important determinants for characterizing the malaria transmission patterns. The vector biting behaviour and longevity, in conjunction with its susceptibity to the parasites, are key elements for understanding the development of the parasite in the mosquito and its transmission to humans. The vector biting and resting behaviour are important in determining the use of insecticides. The information on vector susceptibility to

Plasmodium _and insecticides is predictive of the outcome of transmission possibilities and insecticide control success.

Vector biology studies

The vector biology studies need to be conducted as a necessary complement to the other components of the transmission chain, as it is determined by complex interactions involving humans, parasites and the vectors under different environmental conditions. As such, it becomes very important to characterize the different environmental conditions governing malaria transmission. Due to the existence of several local conditions, it becomes necessary to generate relevant information to characterize the different epidemiological strata from each country and to draw country specific malaria risk assessment maps. Such information can be used for targeted control measures. Several examples exist through Africa and four examples from Mali will be analyzed in this paper.

Examples from Mali:

Bancoumana

An entomological study conducted in the village of Bancoumana (8000 inhabitants, mainly farmers) located 60 km south-west of Bamako in the South Sudan Savanna area of Mali, showed that the vector population, from June 1994 to August 1997, was composed of 98.0% (n=34,682) *Anopheles gambiae s.l*, 2.0% *An.funestus* *An.gambiae s.l.* comprised about 97.0% (n=6226) *An.gambiae s.s* and 3.0% *An.arabiensis* . The *An gambiae s.s* is composed of three chromosomally characterized populations, with 64.3% (n=3770) Mopti chromosomal form, 22.8% Bamako form, 12.9 % Savanna (and hybrids).

The mean monthly mosquito man biting rate for *An.gambiae s.l*. was 79.7, with significant monthly variations (KW, P<0.001). Its highest value was observed in the rainy season in August (150-315 bites/man/month) and the lowest in the dry season, in March (0.06-3.0 bites/man/month)(Figure. 1).

The overall *P.falciparum* circum-sporozoite protein (CSP) infection rate for *An.gambiae s.l* was 3.6% (n=8913). The highest was regularly observed towards the end of the rainy season in October (5.3-9.7%). No significant difference in infection rate was observed between *An.arabiensis* (3.6%, n=196) and *An.gambiae s.s.* (3.7%, n=5914) (chi-square=0.01, P=0.93). But significant difference of the infection rates were observed between the chromosomal forms (chi-square=13.2, P=0.01), with Bamako (5.3%, n=852), and Savanna (5.4%, n=257%) showing higher infection rates than the Mopti form (2.8%, n=2388).

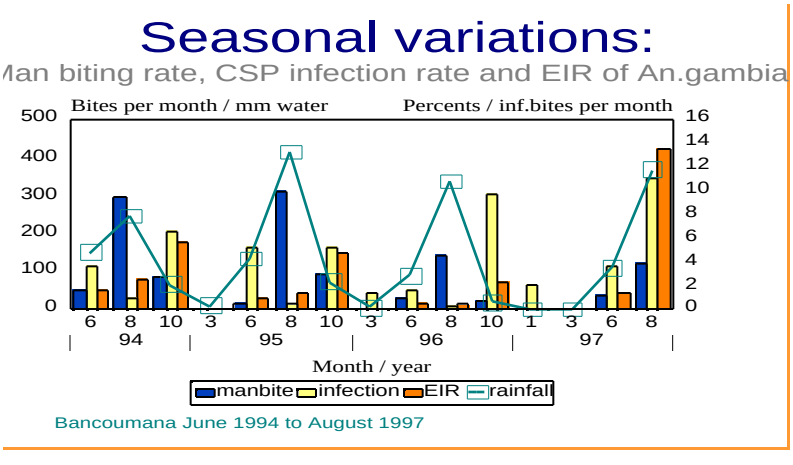


Figure 1. Seasonal variations in man biting rate, CSP infection rate and EIR of *An.gambiae* in Bancoumana (June 1994 to August 1997).

The mean monthly entomological inoculation rate (EIR) was 1.5 infective bites per man per month. The highest values, always observed towards the end of the rainy in October, varied from 4.8 to 5.6. Almost no detectable transmission occurring during the dry season in January/March (0- 0.004). The relative contribution of the chromosomal forms to the EIR were 32.8% for Bamako, 48.8% for Mopti and 18.4% for Savanna/Others.
A stable *Plasmodium falciparum* malaria is transmitted in Bancoumana by the different chromosomal forms of *An.gambiae s.s*, mainly during the rainy season, with more than 75% of transmission and parasite polyclonal infections occurring at the end of the rainy season (in September-October), the same time that the highest incidence of severe malaria cases was observed in children.

Doneguebougou
Monthly entomological studies were conducted from June 1994 to June 1996 in the village of Doneguebougou (700 inhabitants, mainly farmers) located about 32 Kms north-east of Bamako in the North Sudan Savanna area of the Country.

The vector population was composed of *An.funestus* 10% (n=13473) and *An.gambiae s.l.* 90%. Within *An.gambiae s.l.*, *An.gambiae s.s* represented about 70% (n=3199) and prevailed mainly during the rainy season, while *An.arabiensis* represented about 30% and prevailed during the dry season (Figure 2). *An.gambiae s.s.* comprised Mopti (56.0%, n=1547), Bamako (16.1%) and Savanna (20.6%) chromosomal forms, showing significant monthly variations of their frequencies (chi-square=213.4, df=10, P<0.001). The highest relative frequencies of the Bamako and Savanna forms were observed during the rainy season while the Mopti form showed significantly high frequencies throughout the year with the highest during the dry season.

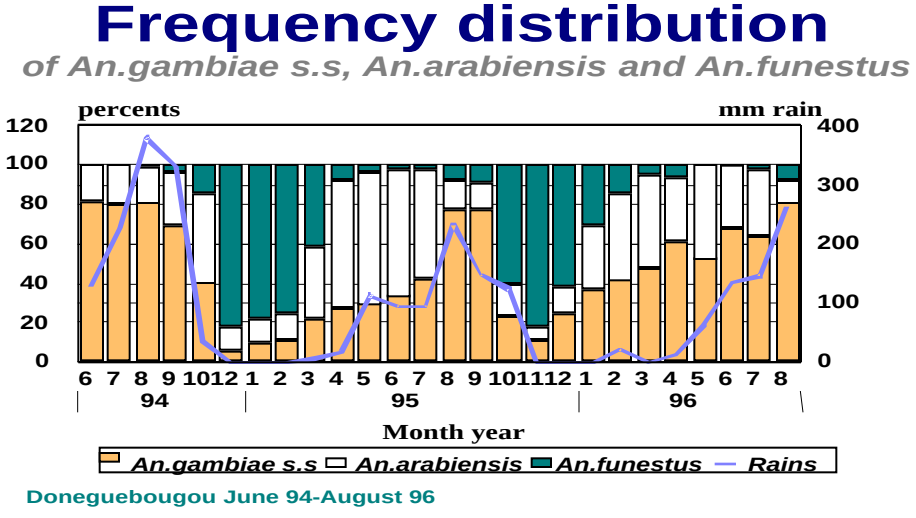


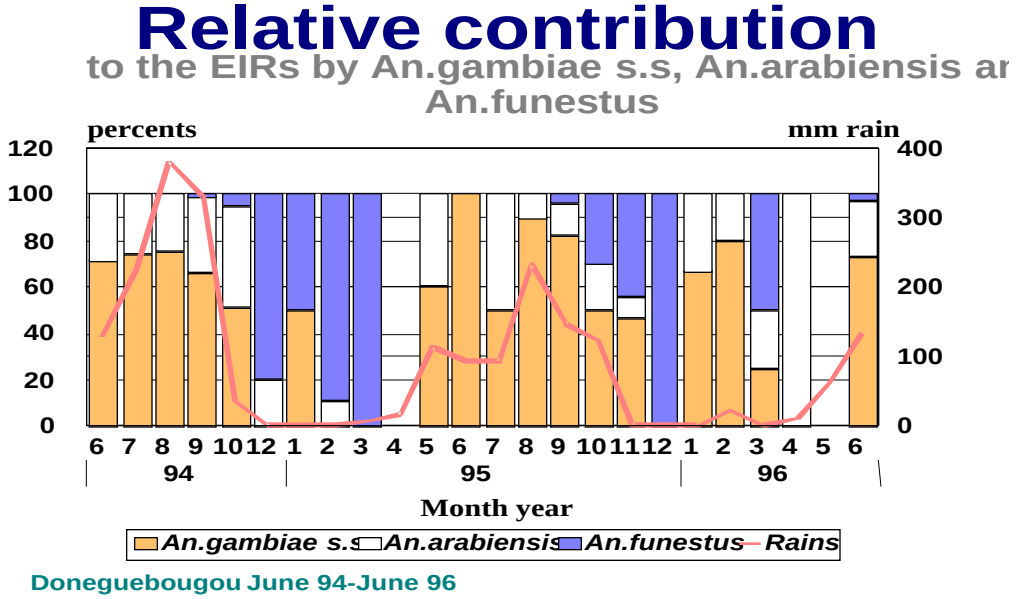
Figure 2. Seasonal variations of the relative frequency distribution of *An.gambiae s.s*, *An.arabiensis* and *An.funestus* in Doneguebougou (June 1994 to August 1996).

The vector annual man-biting rate (for the period from June 1994 to May 1995) was 457.8 for *An.gambiae s.l.*_(peak in rainy season: 87.0) and 41.7 for *An.funestus* (peak in dry cool season: 10.2). The vector CSP infection rates were 6.8%,(n=4052) for An.gambiae s.l and 6.0% (n=1159) for An.funestus, 7.7% (n=947) for *An.arabiensis* and 5.4% (n=2152) for *An.gambiae s.s.* The highest infection rates for *An.gambiae s.l.* (11-20%) being at the end of the rainy season (September-October) and those of *An.funestus* (about 8%) being during the dry cool season.

From June 1994 to May 1995, it was observed that the CSP infection rate of the Bamako (6.8%,n=249) and Savanna (6.9%, n=318) forms were not significantly different (chi-square=0.002, P=0.90), but they were significantly higher than that of the Mopti form (3.5%, n=863) (chi-square=6.5, P=0.01).

For the period from June 94 to May 95, the annual EIR was 29.6 (91.0% of the total) for *An.gambiae s.l* and 2.9 (9%) for *An.funestus.* *An.gambiae s.l.* transmitted mainly during the rainy season (June-October), while *An.funestus* transmitted mainly during the dry cool season (December-February). The EIR for *An.gambiae.s.s* (15.4 infected bites man/year) represented 64.7% and that for *An.arabiensis* (8.4 Infective bites man/year) 35.3% of *An.gambiae s.l.* total EIR (Figure.3). The relative contribution of the chromosomal forms to the total annual man biting rate of *An.gambiae s.s* (341.6 bites man/year), during the period from June 1994-May 1995, would be: 55.0 for Bamako, 70.3 for Savanna, 191.3 for Mopti and 25.0 for the hybrids and recombinants.

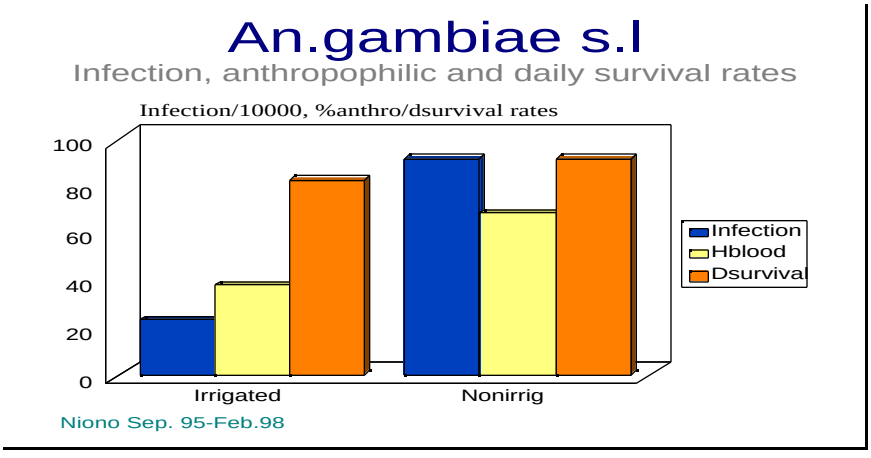
The vectorial system in Doneguebougou is composed of five entities: *An.funestus*, *An.arabiensis* , and the three chromosomal forms of *An.gambiae s.s* (Bamako, Savanna and Mopti). The different entities showed significantly different patterns of population dynamics in strict relation to rainfall. The Bamako and Savanna forms of *An.gambiae s.s* prevailed during the rainy season, the Mopti form in both the rainy and the dry season, *An.arabiensis* during the dry hot season and *An.funestus* during the dry cool season. This represents a kind of partition ("sharing") of the year according to the capabilities of each vector.



Doneguebougou June 94-June 96

Figure 3. Relative contribution of *An.gambiae s.s, An.arabiensis* and *An.funestus* to the EIRs in Doneguebougou (June 1994 to June 1996).

These peculiar differences in population dynamics were observed in the distribution of the man-biting rates, the infection rates and accordingly in the entomological inoculation rates. Thus, malaria transmission occurred throughout the year in close association with the population dynamics of the vector species and chromosomal forms of *An.gambiae* in a "relay pattern" as species and chromosomal forms sequentially predominated at different



times of the year.

Figure. 4. Entomological inoculation rates by *An.gambiae s.l* and *An. funestus* in irrigated and non-irrigated areas of Niono (September 1995- February 1998)

Niono

An entomological study was conducted in three villages of the irrigated rice cultivation area of Niono (about 330 km north-east Bamako) which were compared to three sites in non-irrigated areas, from September 1995 to February 1998, to assess the impact of irrigated rice cultivation on malaria transmission.

The vector population composition was comparable in both irrigated and non-irrigated areas with about 78.0 –99.5% *An.gambiae s.l,* 95% *An.gambiae s.s* and 95% Mopti form. The man-biting rate varied from 252 – 565 bites per man per night in the irrigated areas to 1.5 – 56.0 bites per man per night in the non-irrigated areas. The vector CSP infection rate for *An.gambiae s.l* was 0.23 % (n= 29,001) in the irrigated areas and 0.91% (n=14,396) in the non irrigated areas.

The entomological inoculation rate was 59.1 infective bites per man during the study period in non-irrigated areas and 18.9 in the irrigated areas (Figure. 4). It was observed that the vector anthropophilic rate (human blood index) was higher in the non-irrigated areas (68.1%, n=2348) than in the irrigated areas (37.4%, n=3836). The same pattern was observed for the daily survival rate (non-irrigated:0.91%, n=972 and irrigated: 0.82%, n=1886) (Figure. 5).

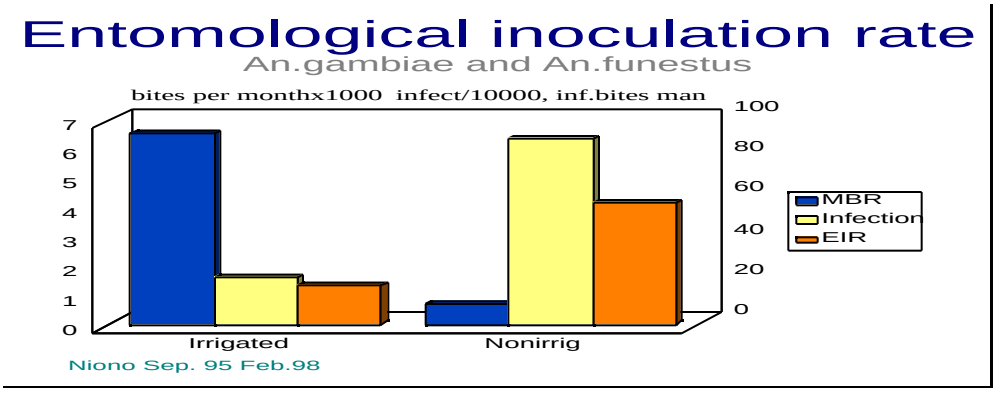
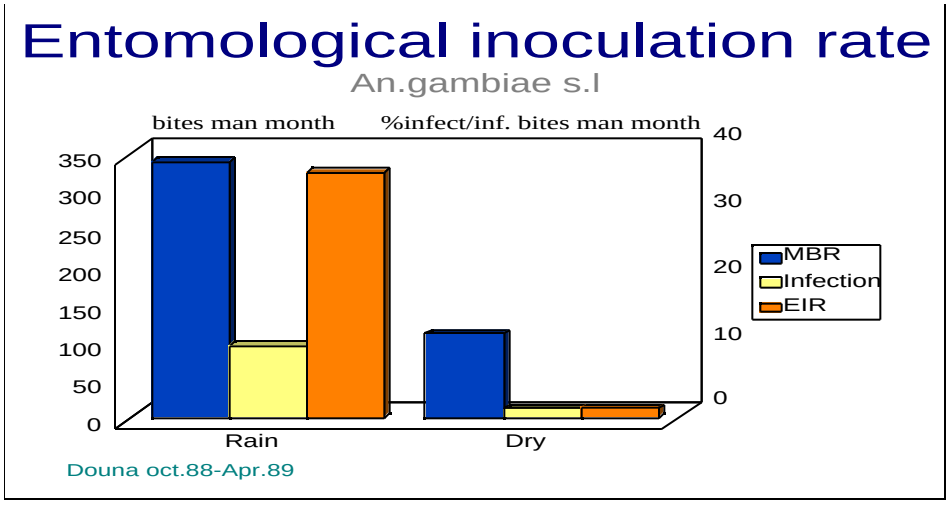


Figure. 5. Infection, anthropophilic and daily survival rates of *An.gambiae s.l* in Niono (September 1995- February 1998)

In comparison to non-irrigated areas, the irrigated rice cultivation areas are characterized by the same vectorial system, higher vector man biting rate and lower vector anthropophilic, CSP infection and entomological inoculation rates. Malaria transmission occurred during the dry season only in the irrigated rice cultivation areas due to double cropping. It appears that even with double cropping, the overall level of malaria transmission in the irrigated rice cultivation areas is lower than in the non-irrigated areas. The irrigated rice cultivation with the double cropping is accountable for the dry season transmission which would not exist otherwise.

Douna (Touré et al, 1996. Med. And Vet. Ent (1996), 10, 197-199)
Entomological studies were conducted during two weeks in October 1988 (at the end of the rainy) and in April 1989 (during the dry season) in the village of Douna (700 inhabitants) located at 285 km north east of Bamako near a floodable area on the banks of the Bani river. *An.gambiae s.s* outnumbered *An.arabiensis* both in October (67% v 33%, n=185) and April (78.2% v 21.8%, n=197). *An.gambiae s.s* was composed of more than 90% of the Mopti chromosomal form. The human blood index was high during both the rainy season (92%, n=86) and the dry season (96%, n=123). There was a significant reduction in the proportion of blood-fed mosquitoes from 55.6% (n=660) in October to 42.2% (n=438) in April. The parous rate in October (80.8%, n=99) was significantly higher than that of April (37.0%, n=154). The man-biting rate decreased from 339 bites per man month in October to 111 in April. The sporozoite rate was higher in October (10.9%, n=202) than in April (1.3%, n=226). The entomological inoculation rate decreased from 36.9 infective bites/man/month in October to 1.5 in April (**Figure 6**). Hence dry season malaria transmission occurred in this village due the dry season larval breeding opportunities offered by the sandy bed of the Bani River.

Figure 6. Entomological inoculation rate of *An.gambiae s.l.* in Douna (October 1988 and April 1989)



How can results be used?

Bancoumana : It is possible to envisage vector control based on intradomiciliary spraying in August (or even How uly depending upon the durability of the insecticide) to cut down the high transmission level observed in September- October. This can be coupled with the careful organization of diagnosis and chemotherapy during that period.

Doneguebougou : The transmission period extends from June to February with two peaks. The transmission of the rainy season is much more important. The scenario suggested for Bancoumana can be applied here, prompting at the same time for the second peak which is very reduced.

Niono : There is a low level of transmission with one peak at the end of the rainy season and one in the dry season. But the nuisance factor due to mosquitoes is very high. The control methods can be based on careful chemotherapy and individual control measures (such as impregnated bed nets).

Douna : There is one peak at the end of the rainy season and a smaller one in the dry season. The scenario suggested for Bancoumana can be applied here for the rainy season peak, prompting at the same time for the second peak that is very reduced. This second peak can also be managed by providing an environmental management system for the riverbed that will avoid the creation of breeding sites.

In general, such results can be used for targeted period for selective control (either chemotherapy or vector control). The problem that remains is the dissemination of these results in time to allow their use by control bodies. One potential solution is the creation of an advisory working group consisting of researchers, control people and other interested/involved groups (inter-sectoral). Such a group will be informed about the results by different means and make suggestions regarding their use. There may be the need for an operational research team to evaluate the efficacy and cost/effectiveness of the suggested measures.

Conclusion

Information on vector biology, ecology and genetics is highly needed to assess malaria transmission patterns and vector characteristics pertinent for control measures. But the available information is insufficiently disseminated and used. Its utilization will necessitate concerted efforts (for example within an advisory working group) between research and control groups to provide information and evidence for policy. The selective integrated control measures must be viewed as a necessary complement to the treatment of cases, and their efficacy and cost/effectiveness may need to be proved by operational research.

Acknowledgements

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-Doneguebougou: WHO/TDR Partnership (grant Ref. T16/181/267 ID 930762)
-Niono: Warda health Consortium (CRDI Canada, Government of Norway, Danida, WHO/PEEM).
-Douna: WHO/TDR/Rockefeller Partnership ID 880289 and the IAEA

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Insecticide Impregnated Bednets for Africa – Implementation, Prospect and Challenges for malaria control

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Introduction

The facts are known. The statistics are mind boggling. Approximately 2.5 billion people worldwide are at risk of contracting malaria. Malaria contributes or causes up to 3 million deaths and up to 500 million clinical cases a year. Most of the deaths occur in sub-Saharan Africa especially amongst children and pregnant women. With regard to children, approximately 4 die every minute, equivalent to 5,000 children dying per day[1].

A few decades ago, malaria seemed to have been tamed. The widespread use of DDT and the discovery of the magical drug chloroquine had almost ensured the elimination of the malaria vector and malaria disease worldwide. However, the slow but sure development of resistance to available insecticides by the vector, the development of resistance to chloroquine and other drugs by the most virulent of the parasite *Plasmodium falciparum* ; climatic and ecological changes; human migration and displacements, economic exploitation of natural and man-made resources for development such as irrigation agriculture from rivers or man-made dams, opening up land for mining; natural disasters and civil conflicts, have turned the tables.

Other factors that have contributed to the resurgence of malaria have included the diminished interest in malaria in the North where it was eradicated in the early sixties, and the chronic lack of proper management; financial resources, inadequate health systems and political will to deal with the problem in the South.

However, in the last four decades, the World Health Organization has been in the forefront of keeping malaria on the world health agenda through various initiatives, culminating in the decisive WHO Global Strategy for Malaria Control adopted at the Amsterdam Conference on Malaria in 1992. This strategy emphasizes (i) promotion of early diagnosis and prompt treatment, (ii) implementation of selective vector control, (iii) early detection, containment and prevention of epidemics[2].

A great deal of effort and significant resources have been invested in research and activities designed to deal with malaria - both for treatment and prevention. Prevention, specifically vector control with one of the available tools, is the subject of this paper. Several tools exist for malaria vector control. These tools include; chemicals such as DDT and other insecticides for residual spraying; environmental management techniques such as eliminating standing waters to reduce vector breeding; biological control such as the use of larvivorous fish and other predators that eat mosquito larvae; applying natural bacterial pathogens to mosquito breeding sites[3] and personal protection by swatting vectors and by use of repellents and mosquito nets.

Mosquito nets have been used for personal protection against mosquitos and other insects for approximately 2000 years[4]. The concept of treating (impregnating) the netting materials to enhance their public health worth is a recent phenomena. Started by soldiers who treated their nets during World War II using juniper oil extracts and DDT, the practice did not spread probably due to the toxicity of the insecticide until the discovery of synthetic pyrethroids which are relatively less toxic [5,6,7]

In the past two decades, several studies have been conducted in Africa, Asia and Latin America to evaluate the impact of insecticide treated materials (nets and curtains) on morbidity[8,9,10,11,12] and their impact on mortality[7,13,14,15,16].

Results on the efficacy of insecticide treated nettings (ITNs) were ably demonstrated by the WHO/TDR funded studies in The Gambia; Kilifi, Kenya; Navrongo, Ghana and Burkina Faso [13,14,15,16]. These were randomized controlled trials which demonstrated that ITNs could reduce all-cause child mortality by 16%-33% in children 6-59 months, and that they are a simple cost-effective public health intervention for malaria control.

Follow-up effectiveness studies on operational issues related to ITNs indicate that, despite the fact that the technology of synthetic pyrethroid treatment of nets/curtains (all referred to as nets) is still evolving, the process has begun and offers great promise for large scale ITN programmes for malaria control in Africa beyond the year 2000. The prospects and challenges for using this technology on a large scale for malaria control in Africa are delineated below.

Insecticide-Treated Nettings (ITN's) : Current Status and Prospects

Current Status

Results from the efficacy trials were made public in early 1996. That ITNs are efficacious i.e. repel and kill mosquitos, reduces the incidence of mild and severe malaria, prevent up to 500,000 deaths a year in Africa alone and are cost-effective as public health interventions, is not in dispute. Studies have even demonstrated that ITNs are much more cost-effective than house-spraying and that people prefer them to spraying[17].

However, not all those at risk from malaria are sleeping under an ITN, or in a shelter/home screened with treated curtains and eaves. The uptake has been slow. Thus there are endemic areas where ITNs are still unknown, are slowly being integrated or included in the repertory of anti-mosquito personal arsenals or have taken off in earnest.

There are numerous reasons for this scenario in general. These are:

- Non-availability and accessability of ITNs in most parts of Africa.
- Lack of resources within countries to acquire the tens of millions of ITNs required to fully benefit those at risk.
- Lack of mechanisms to ensure equitable procurement, distribution and financing where nets exist.
- Lack of political will among governments to treat ITNs as essential public health tools exempt from taxes and tariffs.
- Lack of consensus among scientists on the importance of long-term issues related to ITNs.
- Poor commitment to ITNs from the donor community.

Research efforts have been in the forefront of promoting the implementation of ITNs albeit in small-scale projects. Uptake of ITNs in most countries in Africa is reasonably better where there is a presence of strong research institutions, especially those with committed partners in the North, where there is heavy donor presence and commitment, and where rudimentary policies on malaria control exist. Other driving forces are the non-governmental

organizations, international agencies and more recently, with the support and push from WHO/AFRO, national governments.

For example, out of 42 endemic countries in the African Region, 35 have ITN activities ongoing as part of malaria control. However, information on coverage and impact of ITN on the malaria situation in these countries is currently not available.

So far no large-scale programmes for ITN implementation exist in Africa, and most of the lessons learned are from the small-scale research-oriented projects dotted across the continent. These lessons are valuable and indicate good prospects for the scaling-up of the projects and field trials in the future. These lessons on ITNs relate to effectiveness issues in general, and specifically to technological, implementation and promotional aspects.

Prospects For ITN Programmes Implementation

The promising results demonstrated by the field trials on the efficacy of ITNs in controlled research situations were not seen as ends in themselves. The issue of effectiveness of ITNs in normal field conditions were also accorded high importance and are currently the subject of investigation. An initiative of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and the Canadian International Development Research Centre (IDRC) has over the past three years funded a wide range of projects[18] in different parts of Africa to answer questions on effectiveness. Results for most of the funded projects, the aims of which are to generate evidence-based information to inform implementing bodies, are expected in late 1999.

General and specific observations and lessons from these TDR and other ITN projects are summarised below.

General Perspectives

These have been aptly reviewed by Lines[22] as:-

· Nets are generally accepted even in places where they are not commonly used.
· The insecticide in contrast is a new technology for both users and suppliers.
· In designing an implementation strategy, nets and insecticide must be considered separately.
· Cost is usually a problem and the priority given to net purchase varies widely.
· It is much easier to sell nets (subsidized or otherwise) than to sell insecticide for retreatment.

Thus information on the reality of the situation on the ground is readily available for proposed projects.

Technological Aspects

Improvements of various aspects of the ITN technology-netting and insecticide interactions has been going on. Areas covered include insecticide dosage and packaging improvement to enhance the ease of treatment and retreatment of nets/curtains, which has been observed to be a problem in virtually all ITN projects, especially where it involves cost-recovery. Net treatment/retreating can be done in various ways; pretreatment in factories, coordinated treatment of nets/curtains communally, individual net/curtain retreatment by roving agents or bringing them as needed to treatment points and home treatment where owners treat their

nets/curtains with small quantities of insecticide packaged for domestic use as needed[19]. So far, indications are that people are happy to treat/retreat their ITNs within their own homes because it is convenient and gives them greater control[20]

Two large social marketing projects for ITNs are field testing the commercial viability of the Kits, and more information should be forthcoming. Prospects are positive so far, as industry has seen the potential for these individual dose packs and have started to respond. This seems to be the practical commencement of the private/public collaboration for malaria control.

Widespread promotion and therefore use of permethrin insecticide may lead to the reduced susceptibility to A. gambie of permethrin. This concern prompted research on permethrin resistance to A. gambie, and on the development of simple field tests to allow continuous monitoring of the problem[21].

Preliminary results from Benin and Cote D'Ivore so far indicate that there is resistance in some parts of their study areas to both deltamethrin and permethrin. However, while this resistance in both countries is worrying, it has arisen because of agricultural usage of pesticides and not from the use of insecticide materials related to malaria control. The important finding from these two studies was the demonstration that ITNs are still highly efficacious in their repellency effect against mosquitoes. The epidemiological and operational importance of these finding is that ITNs should be promoted even in areas where resistance has been detected, as there is no conclusive evidence as yet against the use of ITNs in these areas.

However, concerns have been raised elsewhere because of the indication that the repellency effect might contribute to an even larger problem of resistance selection. Studies to confirm/negate this are ongoing (Personal communication Prof. C. Curtis LSHTM).

On the development of simple field tests to monitor permethrin resistance in Anophelines, preliminary results indicate that the bottle assay being tested in Kenya work as well as the WHO kit. Further investigations are still ongoing. Further, WHO/AFRO is working on the standardization of protocols for *P. falciparum* resistance monitoring in the region.

The public health implications of these results augur well for future ITN programmes and should be collated and infused in any proposed ITN implementation plans.

Implementation aspects

The TDR funded projects have covered such areas as appropriate models for implementation/distribution - public, private or mixed; implementation through integration of ITNs with other interventions such as primary health care services (PHC), Mother and Child Health programmes (MCH), economic development projects; the feasibility of different financing mechanisms, and optimization of both net and insecticide distribution and coverage[18.]

Other implementation models tried include; community groups distribution[24,25], women groups implementation (Pers. Com. Akogbeto, Benin), employer based implementation (Pers. Com. Gichohi, AMREF) as well as through the Bamako Initiative approach[16], and of course normal commercial market (implementation) should not be forgotten.

In general, results from completed projects and preliminary findings from ongoing projects show that ITNs can be integrated into other ongoing health or development interventions. However, nets and insecticide do not generally exist in the domain of health commodities but are regarded as one of the arsenals for domestic protection against mosquitoes[22.] These other protections exist in the commercial sector and therefore the element of cost-recovery for personal protection already exists and should not be lost. It is also clear from the projects that ITNs should be paid for and should not be heavily subsidized. Equity matters can be addressed through for example vouchers targeted at special groups such as pregnant women and mothers of young children attending MCH clinics. Vouchers are being tried in an ongoing large social marketing project in Tanzania and the prospects for their use are promising[23.]

Projects looking at social marketing as a model for implementation of either ITNs or retreatment services are indicating that this is a viable model for implementing ITNs and related services into communities.

Social marketing techniques clearly show that the approach can increase people's access to ITNs. The approach has been used in other interventions including oral rehydration therapy and contraceptives and sexually transmitted disease control with promising success. Currently, two large scale ITNs projects in Tanzania[23,27] are ongoing. Together with results from Population Services International (PSI) ITN social marketing programmes in Zimbabwe and Rwanda, these ongoing projects will allow for a better evaluation of the potential of social marketing approach for ITN interventions.

The issue of using the Primary Health Care system as in the Gambia is still under investigation. While it is promising, the same problems that beleaguer other programmes within the health system in general are expected to constrain the implementation of ITNs through this channel.

Large-scale employer based distribution of ITNs has just commenced and information on the viability of the approach should be forthcoming in the near future.

Promotion Aspects

Research into promotion aspects has been geared towards the creation of demand optimisation of distribution to increase coverage, retreatment rates and search for effective promotion channels and appropriate messages. While channels like interpersonal communication are found to be effective, their reach is limited and the mass media widely used radio, television, newspapers, pamphlets and other print are more widely used. The radio reportedly has the widest reach in terms of audience and accessibility.

The discussion above indicates that the prospects for implementation of ITN programmes for malaria control in Africa are good. The challenge is to delineate the roles of each aspect in any successful implementation model.

Challenges For ITN Programmes Implementation

The challenges for ITN programmes implementation arise from the identified prospects. The potential market for nets in Africa is large, as mentioned in a recent WHO meeting[28,] Africa south of the Sahara probably requires at least 30 million nets per year. Clearly, demand for nets far exceed supply. So far, there are no production plants in Africa that can generate

even a quarter of the needed volume. The challenge is to increase production capacity in Africa itself, or to create bulk purchase/import regional centres.

While that is ongoing, national governments should create enabling environments by reducing tariffs and taxes on nets and insecticide together to make the available ITNs accessible cost-wise to as many people as possible. This will allow for the much desired private/public partnership to develop, and will open up more innovative and much needed ITN delivery/distribution systems. To benefit the people from their purchase of an ITN, novel promotion approaches and strategies to enhance proper use of ITNs and, more importantly, the treatment and retreatment of nets must be found. This is the only way to ensure the public health impact of ITNs has been achieved. So far this has been one major constraint in ITN projects, and a big challenge. Who should distribute the insecticide, the commercial private sector or the public sector through its various arms free or at a cost? These questions need to be answered.

In the past, many health intervention programmes have not included mechanisms for the integration of operational research mechanisms to enhance their reach. The challenge is to include the proper monitoring and evaluation of processes and activities in order to disseminate findings widely so as to inform other programmes.

To ensure that a reasonable number of ITNs reach as many people as possible, more commitment from donors, support groups (WHO, UNICEF, BASICS) and other partners must be forthcoming. This could be in the form of financial resources, strategic and technical support and continued support in technology development. Most governments in Africa simply do not have the financial or technical capability of implementing large scale ITN projects.

One of the most important technological aspect areas for which countries will require support, is in the area of developing longer-lasting nets and net-insecticide interaction, which will reduce the need for frequent retreatment, and yet remain cheap. This is a challenge that only sustained continued research can tackle.

Coupled with widespread use of insecticide will be the continued search for simple tests to detect development of resistance to currently used synthetic pyrethroids for net treatment. Detection of resistance is valuable as it allows for an early switch to alternatives unrelated to the insecticide in use [28]. With the prospect of widespread use of do-it-yourself treatment kits for ITNs, the issue of resistance will take a new dimension especially now that new concerns associated with the irreversible effects of synthetic pyrethroids on the developing nervous system are raised.

Other challenges will be the search for imaginative approaches to include communities in the ongoing plan, and to get them to become meaningful partners in what is supposed to not only uplift their quality of life, but save their lives. In the past, communities have been brought into programmes as recipients and this has tended to signal the demise of these programmes before they take off.

The much taunted public/private partnerships for ITNs are another challenge. How committed are the partners to public health, especially where profit is expected in the private

sector? These will require careful quality control of products - both nets and insecticide by an independent body to ensure the public is not duped.

Discussion

In the past two decades research has come a long way in understanding and demonstrating the viability of the use of a simple, cheap technology in malaria control. ITNs are but one tool amongst many, and must continue to be used within an integrated approach with other strategies as adopted in Amsterdam. Reliance on one tool must not occur.

ITN programmes should be delivered in the presence and in conjunction with well functioning clinical management systems. It is heartening to note that the Roll Back Malaria (RBM) project intends to reduce the global burden of malaria through interventions adapted to local needs and the reinforcement of the Health Sector [30] Research on other methods of vector control (non-chemical), early treatment, development of new drugs and issues related to epidemics have to continue in parallel to the implementation of ITN programmes.

More critical to ITNs will be the continued research to improve on the technology and search of optimal financing and delivery methods. The search for alternative chemicals and the monitoring of resistance must also continue, as with strategies that include meaningful public participation.

The task ahead is gigantic. The ITN programmes are being planned for a scenario in Africa that is depressed both by economic globalization and structural adjustment plans. Many countries are faced with financial and/or civil instability, and enormous pressures among others to cut on social expenses including public health. Malaria is essentially a disease of poverty, and war on poverty must be part of the current malaria control strategy. To reach the 80% coverage target aimed for, UNICEF will require concerted efforts by all players - donors, governments, researches and more important, communities. It is clear that ITNs will be distributed like other commercial commodities with subsidies here and there. However, vulnerable groups must always be somehow catered for.

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BREAKOUT SESSIONS: VECTOR BIOLOGY AND CONTROL

Programme

1. Insecticide Treated Nets

Chair: Dr. Awash Teklehaimanot

Rapporteurs: Dr. Don de Savigny, Dr Lucien Manga

Supply and distribution (10 minute presentations)

1. Existing mosquito nets in Africa: A Hidden Resource - Catherine Reed
2. The Gambian Experience: 6 years of running a national bednet treatment programme. - Jane Rowley
3. Public and private partnership for sustainable marketing of insecticide treated materials (ITM'S) in Ghana -Catherine Reed
4. Local productions of bednets in Africa, challenges and experiences from Tanzania - Jane Miller
5. Social marketing for malaria control with insecticide treated nets (KINET Project) – H. Mponda

Re-impregnation (7 minute presentations)

1. Dip it yourself kits: A tool for effective and sustainable treatment and re-treatment of mosquito nets. Caroline Jones
2. Promotion des materiaux impregnés d'insecticides, une activité de service commercialement rentable pour le secteur privé - Jean-Bosco Ouedraogo

Assessment

1. A rapid assessment of ITN programmes in Kenya - Lawrence Muthami
2. Rapid assessment of the coverage of mosquito nets using the cluster sampling technique in the Kasena-Nankana district of northern Ghana - Philip Adongo

2. Vector Biology and Control

Chair: Professor Maureen Coetzee

Rapporteurs: Dr. Luna Kamau, Dr. Ronan Jambou

Goal: to highlight vector biology, ecology and genetic aspects in relation to malaria transmission relevant to plan and implement selective control measures.

Vector population genetics

1. Genetic heterogeneity of African malaria vectors - Didier Fontenille

Vector bionomics and malaria transmission patterns

1. Vector population dynamics and incidence of malaria transmission in Africa - Martin Akogbeto
2. From Anopheline bionomics to malaria transmission: implications for control - Vincent Robert

Abstract Presentations

1. *Plasmodium falciparum* transmission by *Anopheles gambiae* and *Anopheles funestus*in Doneguebougou - Djibril Sangaré
2. The role of four anopheline species (Diptera: Culicidae) in malaria transmission in coastal Tanzania - Emmanuel Temu
3. Le paludisme sur les hautes terres de Madagascar apres cinq annes de lutte par le DDT – Ronan Jambou
4. The 2La paracentric inversion affects levels of differentiation measured using microsatellite loci in *An. gambiae* - Luna Kamau

3. Vector Biology and Control - ITNs and Selective Vector Control

Chair: Dr. Brian Sharp

Rapporteurs: Dr. Andrew Githeko, Dr. Christian Lengeler

1 The development of insecticide resistance in *Anopheles*mosquitoes - Janet Hemingway.

2 Implications of pyrethroid resistance in malaria vectors of Africa - Fabrice Chandre.

3 Influence of resistance of *Anopheles gambiae* to pyrethroids on efficacy of permethrin and deltamethrin treated mosquito nets. First trial in experimental huts in Cote d'Ivoire - Pierre Carnevale.

4 What can be done about the threat of pyrethroid resistance to treated bednets? - Chris Curtis.

5 Genetic crossing experiments of inheritance of permethrin resistance in An. gambiae from Western Kenya - Andrew Githeko

6 Tests for susceptibility of malaria vectors to pyrethroids in an area of Tanzania where these insecticides are used in cotton cultivation - Chris Curtis.

Spraying versus nets

1 Hitting malaria hard below the tropical belt in Africa - Graham White.

2 Insecticide-treated bednets versus residual house spraying in Kwazulu-Natal, South Africa - Abraham Mnzava.

3 Comparisons of house spraying with insecticide treated bednets in Tanzania, India, Pakistan - Chris Curtis.

Summary Report: Vector Biology and Control (Session II)

Introduction

The group felt that the studies on vector biology and their potential use for control measures have not always been taken into account.
From the presentations in this session, the diversity of transmission patterns at different localities underscored a) the importance of these studies for control planning and b) the need for such studies in all malarious regions.These conditions strongly suggest the need for more vector research and control.

The group made the following suggestions:

Research priorities and data needs for control programs

- Operational research to evaluate the efficacy and cost-effectiveness of potential control measures raised from vector biology, ecology and genetic studies.
- Epidemiological and malaria transmission studies to fill gaps in the existing data about transmission patterns, vector susceptibility to insecticides
- Need to take in account all the components of the vectorial systems (including local/secondary vectors) while assessing the transmission patterns, with species identification being an essential starting point.

Constraints to malaria control

- Insufficient communication between research, control and policy making bodies
- Insufficient dissemination and utilization of the existing results
- Gaps in our knowledge at local level about the necessary epidemiological/transmission information
- Lack of efficient mechanism for identifying the problems and setting priorities

Mechanisms for increasing flow of information

- Need for an inventory/compilation of existing information with potential interest for control at country and local levels
- Necessity for quick dissemination of the results in a format adequate for use by control bodies
- Regular consultation between research and control groups

Role of MIM and RBM for links between research and control

- Funding of the relevant operational research and necessary epidemiological/transmission studies.
- Facilitate training of researchers and control personnel

Outcome of comments/discussions during plenary session

- Dr Nabarro representing RBM found that it is essential that vector control be given top priority in areas of unstable malaria and that there is a need to increase at community level the awareness about the role played by mosquitoes in malaria transmission
- Prof. C. Curtis following a discussion in the session, raised the point that in areas of high transmission, the need for vector control may be detrimental rather than beneficial and the issue at whether to have bednets continues to be debated and remained unsolved.

It was also stated (C.Curtis and A. Teklehaimanot) that old data do not indicate dramatic consequences when vector control is stopped e.g. spray program in Pare-Javeta (Tanzania).

Summary Report: ITNs and Selective Vector Control (Session III)

1. Key research priorities

Development of new molecular and biochemical techniques for detecting resistance

Attribute resistance to specific species especially in species complexes

Impact of resistance on repellency, irritability and knock-down

Mapping the distribution of resistance genes and resistant vectors

Assessment of non-pyrethroids for bednets

Management techniques for resistance

2. Implications from current results

Kdr resistance is responsible for broad spectrum cross resistance to all pyrethroids

Some forms of resistance may not be an immediate threat

Need for policy and scientific review to assess the roles of residual spraying and impregnated nets in malaria control.

Impregnated nets still offer protection even in areas where vectors are resistant to permethrin and deltamethrin

Strengthening links between research and control

Control policy should be based on research findings

Research capacity

Need for training in resistance detection using new tools.

COMMUNICATIONS AND CONNECTIVITY

Plenary Presentation

Communications and Connectivity : Global Access to Information
Donald Lindberg

Breakout Sessions

Programme

1. MIM Objectives and Progress to Date
2. Case Studies on Connectivity: Implementation and Inspiration
3. Content and Networking Issues

Summary Report

PLENARY PRESENTATION

Communications and Connectivity : Global Access to Information

Donald A.B. Lindberg, National Library of Medicine, Bethesda, United States of America

Dr. Siegel, ladies and gentlemen, thank you for the kind introduction and the opportunity to address you. Lou Miller has given you much valuable information about how to prepare for and conduct research in Malaria. I'm going to follow his lead and do the same sort of thing--but in the area of computer medicine. We have in our country a professional hockey star named Wayne Gretsky who was asked by a reporter, "How is it that you always are able to skate right to where the hockey puck is?" Gretsky said, "Oh, that's not what I do. I skate to where the puck is going to be." So I think Lou has told you where the field of malaria research is going so you can be there; I'll be doing the same for you about the use of computers in this field.

I would like first to sum up the overall objectives of the Multilateral Initiative on Malaria, as I understand them. These are to develop malaria vaccines and effective drugs, get them into widespread use, and conduct sustainable research for continued progress against this disease. The Communications Working Group, of which the National Library of Medicine (NLM) is a part, is essentially a partnership of all those organizations participating in the MIM. We believe that the Group can play can important role in helping MIM to reach its goals. The Group plans to create an electronic communication capability between African scientists and colleagues anywhere, to afford African scientists access to scientific databases and information services, and to sponsor medical informatics training.

I'm going to structure my remarks to you based on six elements of medical informatics that I think are pertinent to malaria research. These are the computer-based patient record, telemedicine, geographic information systems, scientific databases, network connectivity, and new knowledge representations.

To attain widespread acceptance and use of a computer-based patient record is a tremendously important goal for people in our country. I have been involved with this effort for more than 30 years, and the progress to date hasn't been totally satisfactory. There is a fairly complete system for out-patient practice, but only partial or perhaps, "complete but local" for the hospitalized patient. In the latter case, the computer based patient record consists of clinical lab, radiology, intensive care, physiological measurements and those elements that make up a patient's history and physical examination that can be transcribed into a database. This information, once entered, is generally easily retrieved. I won't say much more about that, other than to emphasize that such records will be extremely useful in your work with patients.

Telemedicine is the second item. This is potentially extremely important for you, although it's a case of looking ahead to where the puck is going to be--when electronic communication in Africa is more advanced than it is now. A few examples from our experience may demonstrate its importance. First, I will show you an example of how a high bandwidth application that uses home cable TV. The individual you see here is a nurse and she is makes telemedicine home health visits to half a dozen places before lunch without leaving her office. Here, she's looking at an elderly person who is homebound; the patient and nurse can see and talk to each other. This has been a very useful system and is popular with patients.

For Africa, more practical than telemedicine that uses high bandwidth applications are those applications that use telephone and modem communications. Here is an example of a simpler, though no less effective, telemedicine application. This is a doctor's clinic in a remote area in one of our western states. We'll assume that there are good practitioners there but not, as it happens, experts in dermatology. This is a teledermatology example that utilized a simple photograph with a commercially available digital camera, just as you see in this photo. The patient has had this rash for several years and has not been able to work. He has seen numerous doctors but not gotten the correct diagnosis. The pictures you see here are so good that a university-based dermatology specialist only took 20 seconds to diagnose the problem and to prescribe a drug that cured the disease in 48 hours. Computer-based record systems are essential to evaluating telemedicine systems such as these so that we can know the cost/benefit.

Here are more informal examples of telemedicine that you might find useful as you do your community-based clinical trials. This laboratory technician is looking through a microscope at a thick blood film with malaria parasites. Obviously this could be used for a teleconsultation. Of course you are familiar with these images, but in many parts of the world and in many medical practices, they are not so familiar with the appearance of malaria. Here is another example, from Bosnia, a soldier suffering a burn. The problem is not to diagnose the burn--his grandmother could that. What is needed is for an expert, in this case in England, to see the burn and then to give advice on the best treatment. I am impressed by the high resolution of the image. It was made by an ordinary digital camera and then appended as an electronic attachment to an e-mail. It may make take a few minutes to transmit over a slow phone line from Bosnia to London. This image is a good rendering of pterygium on an eye, sent from Malta. This is a picture of the leg of sherpa--one of those incredibly able bearers who help climbers in the Himalayas. This telemedicine image was shown to me by a fried to demonstrate how tough sherpas are: the man who had this bad fracture of the fibula crawled 12 kilometers with it to the base camp. I'm now convinced that sherpas are tough.

My third topic is that of Geographical Information Systems (GIS). These are used both to display observations and to see interrelationships and dependencies. Historically, mapped data was used to discover the role of the infamous Broad Street Pump in spreading dysentery in London in the last century. In more recent times the wonderful MARA/ARMA work in the mapping of malaria risk in Africa represents very important and very beautiful work that is happily being presented at this meeting, so I won't describe it other than to express my admiration.

A homegrown example of the use of GIS systems at my own institution can demonstrate its utility. This is a map of the United States and it shows the National Network of Libraries of Medicine. The stars are major Regional Medical Libraries, the little purple dots are 125 Resource Centers, and the tiny dots are local medical libraries of which there are some 4,600. This map shows us geographically how our information resources are distributed. You can see in the succeeding images how our efforts have grown in number and variety in the ten years since the Congress first earmarked specific funds for outreach. One way of looking at the data is to see where the concentrations of MEDLINE users are. We chose to plot them against the boundaries of our Congressional districts. As you can see on the maps, there was much progress in spreading MEDLINE usage between 1989 and 1995, especially to the rural and western areas of the United States. The real value of a geographical information system comes into play when you can input latitude and longitude data for each of the observations.

Certainly a major and successful use of computers in medicine, or medical informatics, is to access scientific databases. Again, I draw attention to MR 4--the Malaria Research Reference Reagents Repository which is run by ATCC and funded by the National Institute of Allergy and Infectious Diseases at the National Institutes of Health. I won't expand on this other than to note it will be tremendously important to access an electronic version of this reagent catalogue.

I will talk briefly about two databases that are relevant to malaria research: MEDLARS and GenBank. The printed version of MEDLINE, the main MEDLARS database, is the Index Medicus, which I am sure many of you are familiar with. People joke about the weight of the annual Index Medicus: it weighs about as much as a man. If we plot the number of articles in MEDLINE (here from 1965 to 1995), it is linear. This rather straight line doesn't look like an information explosion, but if you look within it at a subset of interest to this group—genetics—you will see that it increases at a much faster rate. I should note that MEDLINE searching is available for you at the booth of the Medical Research Council in the exhibition hall.

There you will also be able to search ENTREZ, which is a system for looking at the molecular biology sequence data in combination with MEDLARS. This work was done by our National Center for Biotechnology Information under Dr. David Lipman's direction. You can see in this plot how data is linked, in this case from the published literature at the top, MEDLINE, first to the nucleotide sequences that characterize DNA, then the protein products of those genes, then, after enough information is gathered, to the map of the genes on the chromosomes, and, in many cases the 3-dimensional structure of the protein product. These 3-D structures are very complex, but it is possible to look at the 3-D structure of a protein by downloading an appropriate driver on your computer and then to search for proteins that are similarly structured and find their sources. It is the ability to link all these elements that is the real contribution of GenBank.

Using one article found in the literature, you can expand a search by asking for similar articles; similarly, in GenBank you can ask for DNA patterns that are similar and then link back to the articles that reported them. This is the original GenBank. In 1997 a more advanced version of the same set of linkages was introduced that both links out to the gene expression data (which Lou Miller has already described) and also links to the full-text of articles of some MEDLINE journals. There are 335 journals whose full-text articles so linked at the present time, representing 69 publishers.

This is the home page of the Human Gene Map as it existed in 1996. (There is a current version, but this is easier to show you.) Each of the chromosomes has its own display and then one can click and get a larger display and then can see the genes that have been mapped along that chromosome and from there even go to the sources. In the example I am showing you, there also are explanations, in this case about Alzheimer's disease. The Human Gene Map is noteworthy in that it has been designed for use by patients, families, and the public, as well as by scientists and medical professionals.

My fifth theme is network connectivity. Today, of course, that means the Internet and World Wide Web. Perhaps my most important message to you today is that getting connected is crucial for your scientists and laboratories. The Next Generation Internet that Dr. Siegel

referred to won't be here for several years. It will have a lot more speed, of course, but equally as important for us in the medical area is that it will have guaranteed quality of service and other technical aspects will be greatly improved. To use my earlier analogy, the Next Generation Internet is where the puck's going to be.

Using satellite communication for medical Teaching and research started about 1965. For example, in that year, as you can see in this picture, Baylor televised a live open-heart operation that was received in Geneva. If we fast-forward to 1989, we can see that most of our interactive communication and shifted from satellites and involved computers and the fledgling Internet (the heavy lines on this map show the so-called backbone between major research labs and subsidiary connections connect to smaller centers). I show it to you because this is the last time a computer could ever present such a network rendering; today the map would appear almost solid black with the connections. In 1989 there were fewer than a hundred thousand computers on the Internet, most in the U.S. Today there are almost 150 million and it has grown much faster than predicted in the past several years. Maybe the whole world will soon be covered with computers. It is worth noting that the Internet protocols were developed not by a whole agency or a corporation, but can be attributed to two individuals—Bob Kahn and Vincent Cerf. Everything that has happened since is a result of their scalable design.

Satellite communication is of particular interest to research workers in Africa because, although there is a cable from Cape Town to Europe and the U.S., true continent-wide connectivity will be dependent on evolving networks of satellites. There are several being developed. Iridium, which has already been launched, will have 67 satellites. It was called "Iridium" because the planners originally estimated that its molecular weight—66—would be the number of satellites required. They miscalculated be only one. Another competitor is the GlobalStar System with 48 satellites, ELLIPSO with 16, and the planned ICO Communications System from GM Hughes Electronics with 12. Why the great difference in satellites? The answer doesn't involve geometry or engineering; one need only know that the satellite "footprints" of some of the proposals cover only those countries and cities where the potential monetary return is greatest. Will they address the needs of Africa? That's what has be looked at and that's perhaps where some of the funding agencies should be focusing.

The last topic is new knowledge representation. I am showing you now a bit of the Visible Human anatomical database because it's a new way to view computerized data, in this case 3-dimensional submillemeter representations of a male and female. Although this anatomical information is proving to be tremendously useful in many ways, I can't predict whether it is going to be useful in malaria. But since that is where the puck is going to be, I wanted to show it to you. The Visible Human data were acquired by subjecting male and female cadavers to both electronic imaging techniques and thousands of photographed cross sections, from the head to the toe. The computerized data may then be reassembled in any way one desires to render views of the human anatomy that have never before been seen. There are over a thousand licensees of the data; the images one you are looking now were prepared in Germany. Here is a video clip from another application that uses the Visible Human data to simulate a patient undergoing a bronchoscopy. This is a way for students of medicine and surgery to learn without presenting a danger to a real patient.

A second example of new knowledge representation is the "smartcard," credit-type cards with built in computing capability. Dr. Siegel mentioned my participating on behalf of the U.S. government in the G7 health-related projects. One particular project, being carried out in

France, Germany, and Italy, was of interest to me—the smart card project. This is an area in which Europe is way ahead of the U.S. Those countries have created a standard and have ordered tens of millions of these smartcards to be used in health care both by health care practitioners and by patients. The U.S. is participating in a small way in the smartcard program. One project is the so-called Health Passport Project of the U.S. Western Governors Association. For some 22,000 women and their children these cards will contain pre-school immunization data and data for various health services such as Medicaid, Medicare, health insurance, and other social benefits. The amount of data that can be stored on the smartcard chips is yet to be determined. I believe that we will ultimately have millions available to us.

I am showing you now what is called a "wearable." In this case the computer brains are in a ring. In this picture is John Gage, who is Chief Scientist of Sun Microsystems (and a member of our Board of Regents), and this is a close-up of the ring. The ring has the entire JAVA language, plus all of the encryption technology necessary to send, receive, decode and encrypt messages. You can build this capability into rings, you can put them on pencils, you can even put them on tee-shirts.

Now about the specific work of this connectivity group in the malaria project. Bamako [Mali] is a success--although a lot easier said than done. They now have full access to the Internet, but it took 18 months for that to happen. The methodology is to use a geostationary communication satellite, a microwave link on the ground, and a local area network on site. In the next target, Kenya Medical Research Institute (KEMRI) at Kisian, the scheme is to use a VSAT ground station and a communication satellite to connect an existing LAN to the Internet. In the next site in our schedule, Kilifi, in Kenya, the tradeoff is a microwave link to Mombasa versus VSAT. The next after that will presumably be at the National Institute of Medical Research in Dar es Salaam where there are actually Internet providers, but very sparse telephone connections.

So you can see the only approach that's possible is one that is unique and geared to the requirements of each individual science laboratory. Let me show you how that works. This is a logical diagram of the Mali facility showing the laboratories and the different nodes on the microwave link that goes to the Internet provider. The next slide, KEMRI is the same sort of thing except here you have VSAT. Similar, but not the same.

I want to show you another little wrinkle about the Internet. We're interested in the question: how good are the communications even to big cities and to major research centers and how can we tell? This slide is a summary of a lot of observations, showing how are we doing in Washington, D.C., and Cincinnati in the U.S., the International Research Council in Canada, INSERM in France, DIMDI in Germany, Rome, Tokyo, and London. I actually started this study because friends in London would frequently say to me, in a kidding way, the Internet's wonderful until you Yanks wake up. The implication being that we hog all the bandwidth. But it actually turned out that the Internet got terribly crowded when the British woke up. The problem is almost always local, as you can see on this graph. Inevitably even in the very finest of the labs and with the very finest connections, there still are slow times. Patience is the only answer.

This graph is a proof of my assertion that most of the troubles tend to be local. This is data sent between the National Library of Medicine and a collaborator in Philadelphia, about a hundred miles away. Not very far with everybody having pretty good connections, except that this is to a home using a modem such as you would here. You'll notice the delay on the last

link about a hundred yards from the person's house. All the rest of you can go around the world and not experience such a delay until you get to that house. The problems usually are local, but on the other hand that means that they're soluble.

I recommend to you an incredibly interesting book called 'The Victorian Internet' by Tom Standage. He takes us back a hundred years, when the high technology was the teletype, when Morse was inventing the Morse Code and competing with inventors in England and in France, when he was being overtaken by a young man named Thomas Edison, who actually made the invention that let four teletype signals travel on the same line. In some ways, the circumstances were similar to the Internet now. First, much of the developments was fundamentally motivated by business. Although our first major network was called the NREN, the National Research and Education Network, nevertheless I would maintain that today most of the investment is by business people for business. The teletype certainly had that in mind. Another factor was that everybody said it will never work. The growth at first was slower than the enthusiasts thought, but soon it was much faster than even the most optimistic thought possible. The same is true of the Internet.

Because of its use in business and the military, 85% of teletype traffic a hundred years ago was encrypted. As you know, this is a major political debate now. Will certain countries allow these encryption algorithms where they are afraid that criminals will get them? This is a hundred-year-old argument. In all cases, the countries had ultimately to yield because they simply couldn't keep up with the amount of encryption that was already occurring.

The writings at the time essentially said the strife between the nations is over. Mankind will see brotherhood, because the teletype allows a close and immediate contact between people. Well, it didn't quite work out that way, but maybe Internet will work better for us. There were great expectations then; there are great expectations now.

As to the business of genome sequences, more than half of the protein coding for the human genome is mapped already. Can this be done in malaria? To know not only just the sequences but the meaning of those genes, the gene expression and the phases of the parasite and the phases of the disease, the interactions between those, will be a tremendously big job, and it will be dependent upon the contributions of everyone in this room and everyone in your laboratories.

So I wish you good luck in the endeavor. It's a wonderful enterprise and you are to be congratulated for your progress. Thank you for letting me be with you.

BREAKOUT SESSIONS: COMMUNICATIONS AND CONNECTIVITY

Programme

1. MIM Objectives and Progress to Date

Chair: Julia Royall

Rapporteur: Dr Rose Leke

Panel: Dr Elliot Siegel, Dr. Andrew Kitua, Dr. Yeya Touré, Erik Schoute, Dr Rose Leke, Brett Lowe

1. Objectives and Update of the MIM Communications Working Group – Elliot Siegel.
2. Overview of sites and objectives of the first phase, implementation, training and capacity building, documentation, etc - Julia Royall.
3. Introduction of panel, each of whom will talk for 15 minutes about specific aspects of their sites, giving examples of how they have achieved or will achieve MIM objectives. Q&A, Discussion.

2. Case Studies on Connectivity: Implementation and Inspiration.

Chair: Mike Jensen

Rapporteur: Mark Bennett

Panel: Chris Whalen, Bill Sangiwa, Tom Oluoch, Erik Schoute, Bob Hata

1. Connectivity in Africa, the challenges and lessons learned - Mike Jensen/Mark Bennett.
2. "Nuts and bolts" cases of problem solving - Panel (see above).
3. Funding issues - Bobak Rezaian and Bob Hata.

3. Content and Networking Issues.

Chair: Dr J.A. Koos Louw

Rapporteur: Dr Ben Fouche

Panel: Dr Ray Cypess, Dr. Yimin Wu, Ms Nomfundo Luke, Dr Ben Fouche, Dr Chris Seebregts, Dr Barend Mons, Helga Patrikios, Regina Shakakata

1. Introduction - Koos Louw (10 minutes)
2. New malaria repository - Ray Cypess (20 minutes)
3. MEDLARS databases as a source of bibliographical information on malaria research - Nomfundo Luke (15 minutes)
4. The concept of a Knowledge Network - Ben Fouche (15 minutes)
5. The Health Knowledge Network - Chris Seebregts (20 minutes)
6. The SHARED database - Barend Mons (15 minutes)
7. Issues from the librarian's perspective - Helga Patrikios, Regina Shakakata

General discussion on the value of these resources and needs to be addressed.
Speakers constitute a panel.

See http://www.mimcom.net for additional information and links

Communication and Connectivity : Summary Report

Introduction

The overarching rubric for the Communications and Connectivity track is this: How can the MIM Communications Working Group (NLM and other partner institutions) help African scientists (initially at sites conducting research and control activities in Mali, Kenya, Tanzania, and Cameroon) gain full access to the Internet and contribute ultimately to the reduction of morbidity and mortality of malaria?

The next question is not what might a researcher do with increased access, but rather, what is it that a researcher is trying to do but can't do, given current access? In other words, the project is focused initially on the researcher and her/his particular challenges in being part of the international malaria research community. It is important to emphasize the human nature factor at this point -- how can a researcher's willingness to engage with information technology be made worthwhile? What is the reward, the incentive? This may seem almost too obvious to state, but at the end of the day, isn't this the critical factor (given that the technology is up and running, of course!)

Another question to be addressed is this: How can the communication and information collection and exchange be South - North and South - South as well as North - South? And how, with the South's full participation, might the traditional models of the North be changed? It shouldn't be an issue of whether to superimpose a Northern model **or** that the indigenous model is always the superior route. Either way, we risk condescension to the possibilities information technology offers and see it simply as a way to do what we've always done, only "louder and faster." Instead, we might look for a whole new way of doing things beyond either of these alternatives.

This is where a malaria research network project is positioned to serve a vital purpose -- that is, provide the opportunity for colleagues in industrialized and developing countries to work together to create a truly new paradigm in research and development rather than simply perpetuate old models.
This track provided an opportunity for the MIM Communications Working Group, chaired by NLM, to report on its activities since the communications need was identified at the Dakar Conference in 1997: "to enhance the capacity of African scientists to communicate electronically with colleagues in Africa and the North, and to access needed scientific information from libraries, remote databases, and on the Internet." (Dakar Final Report)

NLM has carried out site assessments and technical consultations at malaria research centers in the four countries selected for the first phase; funded the purchase of telecommunications equipment, training, and library infrastructure development; and documented successful implementation at the Malaria Research and Training Center at the University of Mali in Bamako.

The Communications and Connectivity track comprised

“Global Access to Information”, a plenary talk by Donald AB Lindberg,

1. Director, NLM, based on six elements of medical informatics pertinent to malaria research: the computer-based patient record, telemedicine, geographic information systems, scientific databases, network connectivity, and new knowledge representations;

2. Three breakout sessions focussing on Communications and Connectivity from three different perspectives: that of the scientists whose work a research network will support, the technical experts who advise on technology to be used and carry out the actual implementation, and the information specialists who rethink traditional sources of information and vehicles for its dissemination and imagine new ones;
3. Individual consultations in which country representatives had an opportunity to talk directly with technical experts about the present capabilities of their sites as related to their research.
4. A booth for demonstration and training in Medline and other databases, staffed by the Medical Research Council of South Africa.

Breakout 1: MIM Objectives and Progress to Date

Introduction

The first session set forth the mandate of the Communications Working Group and the action plan. Researchers from Tanzania, Kenya, Cameroon, and Mali talked about their communications problems, needs, and identified solutions.

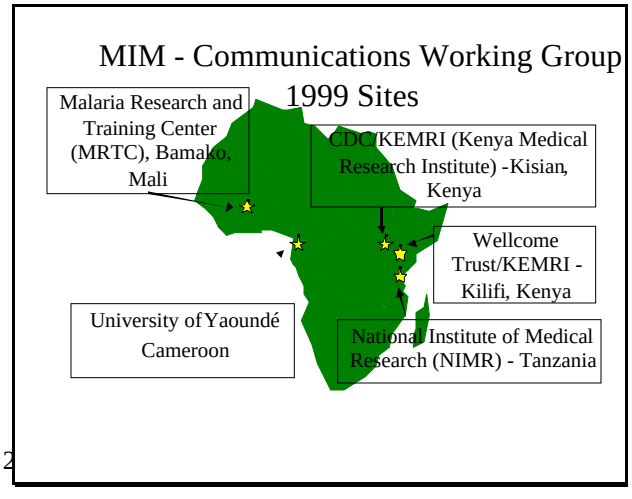
The Communications Working Group's objectives are to:

- Enhance communications between African scientists and with colleagues worldwide; create telecommunications links to the Internet that permit African scientists to participate fully in the work of the international research community;
- Provide access to electronic databases and networks in support of research (e.g., MEDLINE, BIOSIS, GenBank, Malaria Research Repository; ATCC, relevant World Wide Web sites, GIS, MARA, SHARED);
- Support informatics training and knowledge management skills (including library infrastructure development, document delivery);
- Promote interaction between scientists and communities involved in research and control.

To respond to this mandate, NLM has led the group to:

- Identify and prioritize targets of opportunity in African malaria research sites;
- Identify needs of local scientific community requiring enhanced communications capabilities in support of malaria research and control activities
- Assess status of local information and communications technology, networking infrastructure, and on-site expertise capable of maintaining the technology and supporting users;
- Train users in equipment operation and the skills needed to utilize newly accessible electronic information resources, including local library services;
- Establish means to pay for new Internet connectivity and use on an ongoing basis, and to upgrade its capabilities as needed.

At the Wellcome Trust funders meeting in London in November 1997, initial target sites were selected in Mali, Senegal, Kenya, and Tanzania; each receives MIM research funding and has strong champions for communications. In January 1998, NLM convened the first CWG meeting at NLM/NIH in Bethesda, MD. to agree on objectives, ratify action plan, and receive



preliminary reports on 'connectivity, content and training' at first phase sites.

Implementation Strategy

- Focus on locations having high scientific priority for MIM research funding;
- Engage research and donor agencies in funding communications as a cost of research;
- Identify viable technical solutions to support Internet connectivity, consistent with research needs, local geography, and affordability. Beyond traditional telephone dial-up connections which can be slow, unreliable, and costly, more dependable solutions can include microwave, a point to point option that uses radio waves, and VSAT (very small aperture terminal) which communicates via a geostationary satellite. Obtaining regulatory approval in some African countries can be a significant impediment for VSAT and other wireless solutions.
- Foster collaborations with local academic, governmental and business interests telematics is essential for national development;
- Attract new partners to MIM.

CWG Partners:

- African malaria research scientists and their students
- African governmental agencies and academic institutions
- Key international research and donor agencies
  NIH (NLM, NIAID, FIC), Institut Pasteur, CDC, Walter Reed,
  WHO (TDR, AFRO), Wellcome Trust, Burroughs Wellcome Fund, World Bank, USAID
- African and international medical library community
- African and international telecommunications consultants

Breakout 2: Case Studies on Connectivity: Implementation and Inspiration

Introduction

The second panel tackled the problem of communications and connectivity from a technical point of view. To understand the difficulties experienced by malaria researchers in obtaining full Internet connectivity and access to the resources of colleagues internationally and the WorldWide Web, it is necessary to take into account the history thus far of Internet development in Africa. That said, it is then possible to position the technical alternatives

available to research sites desiring increased access. Finally, the discussion is not complete without strategies for funding and implementation.

Although most African countries now have an Internet connection in the capital cities, widespread access has been constrained by low density of telephone lines, aging infrastructure, expensive international connections for Internet Service Providers, tight regulatory control over telecommunications and Internet market by government monopolies. In addition, there are problems with access to a stable power supply, maintenance of computer equipment, and natural hazards such as lightning. The challenge for malaria research sites is to connect to the Internet either locally through an Internet Service Provider (via telephone or radio waves) or internationally via satellite. To make this connection, the site must take into account the nature of the work it is not able to carry out due to poor communications as well as the geographic makeup of the area. These factors govern which available technology can best improve the ability of scientists to do research vital to combating the mortality and morbidity of malaria and, over the long term, reduce total communications costs.

The following offer a technical overview of the initial sites

- *Malaria Research and Training Center, Bamako, Mali* with NIAID, Faculty of Medicine/University of Mali, World Bank and USAID;

Installed direct microwave connection (Cylink 64SMP) between MRTC and the ISP (56kbps service) in Bamako. LAN, e-mail, and proxy server supports researchers, students and visiting scientists. New configuration replaces inadequate, costly and unreliable dial-up telephone service. Initial cost shared by NIAID and World Bank, annual cost of Internet Service Provider covered by NIAID.

NLM and World Bank plan enhancement of existing library facility; and institutional collaboration with US libraries (DOCLINE) enabling document delivery services in Mali and to colleagues in West Africa region.

- *CDC/KEMRI, Kisian, Kenya* : with the Centers for Disease Control, Kenya Medical Research Institute, and Walter Reed Army Institute of Research;

Existing LAN and 80 PCs on site. Dialup connection is poor. VSAT link is recommended technical solution. Awaiting written approval from Kenyan authorities to install and operate VSAT.* NLM agrees to cover initial cost of equipment, installation, and training; CDC to pay recurring annual cost.

For this site, VSAT costs are on the order of $25K upwards for equipment purchase and installation, and $25K/year for operating costs for 64kbs ($40K for guaranteed) service. This compares with conventional telephone and dial-up email (often poor quality) that can exceed $30K/year.

- *Wellcome Trust/KEMRI, Kilifi, Kenya* : with the Wellcome Trust, Kenya Medical Research Institute, and Oxford University;

New LAN presently being installed linking 60 computers. Expensive dialup service to Internet Service Provider in Mombassa for low speed email; web access inadequate. VSAT groundstation recommended; installation and annual operating costs same as for Kisian, with services shared from the same vendor. NLM is prepared to cost-share (as indicated above in Kisian) with the Wellcome Trust, pending regulatory approval by the Kenya PTT.

* ***Update since Durban** : The research sites at Kisian and Kilifi were connected via satelite (vsat) in July 1999 and have full access to data, voice and image.

- National Institute for Medical Research, Dar-es-Salaam, Ifakara, and Amani, Tanzania ;

A local Internet Service Provider currently serves Dar-es-Salaam headquarters. Limited Internet dialup accounts presently in use. Major malaria research site in rural Ifakara, 250km from Dar, telephone lines are sparse and unreliable; sporadic email via Fidonet; dialup Internet not feasible. Amani houses focal point for the East African Network on Antimalarial Drug Resistance, but no dialup email or Internet links possible with present telephone service. Tanzania has liberal telecommunications policies and a large ISP (CyberTwiga) in Dar. A one-time hardware cost to connect to their wireless Ethernet (offering a 2Mbps connection) is relatively modest, as are the expected operating costs. VSAT is recommended for Ifakara and Amani, with equipment installation costs typical for this technology, but lower recurring costs due to smaller size of these sites. LAN and PC upgrades should also be anticipated. NLM is prepared to cost-share in Tanzania if a suitable entity can be identified to fund the annual operating costs.

- Institut Pasteur, Dakar, Senegal

Full Internet service established and supported financially by Pasteur; technical specifications not defined.

- University of Yaounde, Cameroon

Site assessment recently completed; microwave and VSAT options both under consideration as means to connect the remote malaria research site to the university's campus-wide fiber-optic network.

- University of Zimbabwe, Harare, Zimbabwe

Location of major sub-Saharan African medical library, but with unreliable Internet service at the university. Plan to connect library to VSAT link at newly established WHO/AFRO headquarters. NLM collaborating to enhance malaria-relevant literature holdings, and support document delivery to East Africa region as a DOCLINE library.Out of discussion during and after the session, new candidate sites for connectivity were identified in Ghana and Nigeria.

Organizational Considerations

The CWG technical team at the MIM African Malaria Conference in Durban had a number of lengthy discussions regarding the technical functions that would need to be handled centrally. The following summarises those discussions:

With the MIM Communications Working Group's commitment to assisting with the provision of Internet connectivity to a number of malaria research sites in Africa it is suggested that there are various centralized functions which will need to be carried out on an ongoing basis.

While it is generally beyond the scope of the Communications Working Group's current remit to fund recurrent costs (research sites being provided with capital costs for equipment, installation, and training) there are some issues that will arise on a continuing basis that need to be addressed. These issues pertain to all sites that will be connected, and therefore a continuing input is needed to maintain operational status. This is particularly true given the likelihood that a number of MIM sites will share a common satellite connection, which will need co-ordination.

Who funds this continuing work and who carries out the work is yet to be considered, but the following may be required of such a coordinative body (further details found in the Technical Appendix):

- Map of all current malaria research sites against their actual connectivity, and that which would be potentially available in their locality.
- Provide advice on potential connectivity and a full feasibility to commissioning service for different kinds of Internet access at any MIM site.
- Take advantage of economies of scale not available to sites operating independently. This will provide reduced operating costs and thus ensure greater sustainability.
- Identify problems associated with gaining and maintaining Internet access and a methodology for overcoming those problems.
- Build up an infrastructure, which will have a ripple effect across the health sector, and not just to MIM sites.
- Provide and maintain a set of standards that will apply across all data systems at MIM sites.
- Provide guidelines for librarians and promote sharing of resources (document delivery).
- Build up a web-based resource appropriate to MIM sites.
- Train an effective user base (for both technical and information users).
- Create a reliable geographical resource and personnel data, which will allow dissemination of information and resources to any MIM site by the most expedient means.
- Promote communication both between MIM sites and to and from other relevant parties.

Summary

Much of the above work can be provided remotely, and could be undertaken by a number of different persons / companies / groups. However, there is clearly an advantage to an overall common coordinated approach, whatever form that takes.

It is hoped that commitment to the connectivity of MIM sites to the Internet can be followed up by ongoing support that will maximise the use of that most valuable asset, and in turn ensure that the greatest possible number of researchers can gain access to the facility.

Breakout 3: Content and Networking Issues

Introduction

The third session challenged the conference to avoid an over-emphasis on technology and to capitalize on putting people in touch with other relevant people and providing them with the necessary information and knowledge resources. Presentations and discussion focused on the value of information flow and interaction among people made possible by Internet connectivity, including appropriate information systems that allow such interaction in a virtual environment and further knowledge transfer and innovation.

Presentations covered a wide range of territory: from ATCC's new malaria repository to the SHARED database; from using MEDLARS databases as a source of bibliographical information on malaria research to the conceptual framework of a knowledge network to the myriad of issues surrounding document delivery. The Medical Research Council of South Africa proposed the Health Knowledge Network concept as an online resource and gateway for malaria information and knowledge management. Dr. Louw spoke of a Knowledge Network that "can serve as a repository for malaria information, allow knowledge discovery and provide a virtual environment for interaction among malaria researchers." The MRC also proposed a new role for itself as DOCLINE library serving southern Africa.

Dr Ben Fouche further highlighted the concept of knowledge networks in general. Based on the principles of knowledge management and utilizing modern information and

communication technologies, such initiatives will be underpinning innovation in the various fields of focus.
Dr Chris Seebregts provided insight into the architectural design of the MRC's developing Health Knowledge Network. One of the content modules of this Network will be a malaria information repository.
Ms Nomfundo Luke alluded to the role of library services in unlocking various available malaria information sources. Her team would like to collaborate with the NLM in providing a more extensive information service to health researchers. In this regard the MRC would like to become a DOCLINE library and to network with other relevant libraries in southern Africa.

SHARED

B. Mons, Jan van ´t Land, Klaudia Werth, Cornelius Oepen, Mario Diwersy, Martin Schmidt, Michael Wahl, & Erik van Mulligen.

What can SHARED mean for MIM ?

With the increasing volume and complexity of human knowledge, economies of scale and networking become more important in scientific practice every day. Effective knowledge management and tools to support that process are therefore of increasing interest, not only to research policy makers, but also to individual scientists.
Also in the field of malaria an overwhelming amount of data sets are being stored in databases and publications all over the world. These data are however, not optimally available and accessible, especially to those colleagues working in areas where communication technology is not up to date.

Databases without the in-built feature of connectivity will rapidly become outdated and obsolete in a culture of electronic knowledge management and communication. Database Driven Communication is now becoming the norm, and organisations which will not follow this trend run the risk of becoming isolated from the mainstream of communication and stuck in the interim period of information overload which is currently the major shortcoming of the Web. Especially for colleagues working in Developing Regions, where connectivity is sometimes poor and on-line time exceedingly expensive, there is a real danger that ICT will widen the gap between those who have access to information and those who do not.

In the scope of an EC supported international Concerted Action named SHARED, a new approach to the international hurdles for effective knowledge management has been developed in partnership with stakeholders in Developing Countries. As a result the concept and the technology supporting the SHARED concept feature a number of aspects which make the system one of the most straightforward and user friendly tools for targeted exchange of information over wide spread networks, ranging from scientific networks to multinational, societal and political groupings.

The concept is based on the latest web technology and combines a number of innovative features to enable Automated Web-based Archive Retrieval and Exchange (the supporting data management technology is named AWARE). It's all about increasing alertness and awareness of key people involved in a common health related process, with emphasis on getting relevant (and *only* relevant) information to the right person with minimum of effort and a maximum of efficiency. More effective use of scarce resources, prevention of duplication and optimal awareness of opportunities within the network as well as on the Internet is the main added

value of the system. Also it has a very pragmatic and user friendly approach to collection and quality management of the underlying data sets.

The system allows fully decentralised management of the supporting relational database, which in turn is set up to drive efficient communication of selected knowledge and direct it to the right people.

Although developed for International Health Research in general, the system can be integrally applied for the exchange and wide dissemination of information on a particular disease, like malaria. It meanwhile allows exchange across disciplines, which is very important for the realisation of some of the goals of the Multilateral Initiative on Malaria (MIM) and the Roll Back Malaria Movement (RBM). The system has meanwhile attracted wide attention in other fields, including Agricultural research for development, Electronic Publishing, and a variety of other ICT applications for other international activities.

It is the intention of the SHARED initiative to establish in 1999 an international, representative board where stakeholders in health research for development can act as a guiding committee for the further development of the SHARED concept and the links with other relevant knowledge based initiatives, such as databases on materials, publications and discussion groups on the WWW. Throughout this development process SHARED will fully keep in focus the specific needs for collaboration with colleagues in Developing Countries. In fact they will be intimately involved in the process. Close collaboration with the NLM-led initiatives on actual connectivity in Africa are foreseen in the scope of the MIM and collaboration with the Malaria Foundation International (MFI) concentrates on establishing a world-wide discussion platform with full inter-linking of relevant projects, organisations involved, people involved and publications.

Underlying concepts

- Interactive Indexing

One of the major impediments of free text published in electronic environments is proper indexing. In most sites, the user entering the text file is asked to pick keywords from a long list that hardly ever fits perfectly and this part of the entry process is very time consuming, typically well over a minute for the text of 400 words.

The IKA software module of the AWARE system is a very elegant and swift solution to that problem.
It is a modular system consisting of a lexical tool, which normalises all keywords, a comparative module, which compares the list of recognised words to a third module which is a preconceived thesaurus, which in the case of UMLS also links those words to concepts. The system also recognises logical clusters of words and links them to medical concepts. All words and concepts which are shared between the text and the thesaurus are analysed by the fourth, statistical, module, which ranks the keywords in conceived order of discriminating value, based on established algorithms.

The system can be programmed centrally and modified by the user to return a keyword/concept list ranging from best 5 to best 50 terms characterising the text. This entire procedure takes around 1 second for a text of 400 words.

It is obviously unavoidable that keywords forming part of a negation or other keywords judged as irrelevant or misleading by the user will be contained in the list. The list is therefore returned to the user in the format where the user can easily disable undesired keywords

through clicking the box in front of the term which is ticked for *acceptance* by default. All words and concepts left enabled will be accepted as keywords. Manual addition of keywords will be optional.

All other search and linking features can subsequently be operated based on full text or, alternatively, on accepted keywords only.
Wider use of IKA than just for the intra- or Internet application of individual networks is foreseen and can be actively promoted by the users in a certain area of interest. In the health field direct linking with literature databases indexed with MesH terms (such as Medline) can be directly linked to texts in SHARED and other health related web environments using the system.

The SHARED technology is based on the concept of wide-spread and complex data sets: world-wide, projects, people and organisations involved in international health research and development. Therefore, a fully equipped management tool has been developed which is both simple, user friendly and highly effective. Anyone with an Internet account can enter information in the system without the need for a password. During the entry process, the user is in actual interaction with the database and is therefore not entering any data which might already be present in the data base. As the system is centred around people, both in the context of their activities and their organisations, the principle personal information is the Electronic Business Card of the person. This EBC is essentially comparable with a regular business card with the important added value that it has WWW. and e-mail addresses hyper linked for direct access.

Organisations are also listed in this way (interactively with personal data) and the input tool allows information to be added, such as Mandate, Activities, Procedures, Expertise and other relevant fields. All these text are indexed with IKA upon entry. Activities and expertise information on people (either in the form of mini-CV's or interactively derived from project texts linked to their ECB or the organisation they work for) will be used to search for people with specific expertise or interests.

- Decentralised quality control
The interactive input of data prevents most of the unintentional undesired data submission, such as duplicate projects, misspelled names leading to double records etc. However, the occasional false data unintentionally coming in or intentional irrelevant data will be filtered out through the decentralised quality control tool of SHARED technology. Actually, all data stay in unapproved records, which are not retrievable by regular users, until one of the authorised data managers of the network has approved the data. Datamanagers can be centrally authorised for specified subsets of data in the system (for example a national focal point or an organisational focal point. All data coming in will be allocated to a data manager either by choice of the user entering the data or by default (country of origin for example)

All data in the subset of a manager can be fully managed by that person and by choice also by one or more alternative responsible persons.

All these management activities do not require more computer skills of the manager than needed to browse the Internet with a regular browser. Although organisations or networks can choose to operate the system with a central server linked to an unlimited number of mirror sites, in essence the system can be implemented at one central server and all management can be performed after logging in at a single Internet or Intranet address.

In countries where on-line time is scarce or overly expensive, the system allows managers to operate mostly off line if they have a mirror server and update the central database with information batches at regular intervals.

-Advanced Search Options

The system has a unique search tool, which allows several features in addition to classical (full text) search engines.

First off all by default, the engine will only look for a set of keywords identified by IKA. This can also work for actual search activities. The user can briefly describe the interest and find all texts in SHARED that match the profile of the query, without the need to fill complex sets of fields in the menu of the search engine. In addition, the advanced search option allows the composition of personal search profiles, for example, all projects on malaria and pregnancy in West Africa funded by the European Commission and/or NIH, which are implemented by universities can be selected.

Once selections have been made, all possible contact information is made operational within the system, so that names of organisations lead to their intermediate descriptive page in SHARED and subsequently to their web sites, e-mails are clickable, and collective mailings can be accommodated in the course of 1999.

All user-side operations in SHARED are freely accessible to all, with the exception of collective mailings, to prevent commercial use. This feature will be password protected an the right to assign passwords will probably lie at the focal point level. The access to the central SHARED management tool is restricted to registered focal points.

In the field of Malaria SHARED intends to work with all major exisiting networking activities and with most of them advanced contacts on collaboration are made. These include: MIM, RBM, MFI, COHRED, INCLEN, INDEPTH, MARA, AMVTN and others. Wherever these networks include functional knowledge nodes with good computer facilities and connectivity, SHARED will support the involvement of these nodes in the set up of a comprehensive knowledge network for malaria research and implementation projects, with strong links to other disciplines.

The latest developments in SHARED and various manuals can be downloaded form the SHARED site at: http://www.shared.de/newsletter/news3.html

Everyone can put in a requests to start the process to become a SHARED national or organisational focal point by sending an e-mail to: SHARED@nwo.nl.

ATCC

ATCC is a global nonprofit bioscience organization that provides biological products, technical services, and educational programs to private industry, government, and academic organizations around the world. The mission of the ATCC is to acquire, authenticate, preserve, develop, and distribute biological materials, information, technology, intellectual property, and standards for the advancement, validation, and application of scientific knowledge.

Malaria Research and Reference Reagent Repository (MR4) project with National Institute of Allergy and Infectious Diseases (NIAID) at NIH will improve access to parasite, vector, and human host reagents and standardize assays using well characterized, renewable reagents.

- Acquisition

MR4 will actively solicit and acquire valuable reagents through a broad program of both print and electronic communication with the scientific community

- Authentication
MR4 will implement characterization, standardization, and documentation of reagents. The depositors' original data and published references on the reagent will be used as quality control criteria

- Preservation, Production, and Development
MR4 will preserve and authenticate reagents and data. Renewable reagents will be reproduced as needed and re-authenticated before distribution.

- Distribution
MR4 will distribute reagents to registered, qualified investigators throughout the world for only the cost of shipping.

Five Month Accomplishments

Advisory board formation and meeting
Operational procedure: AAPPDD approach
User access protocols: registration, depositing and requesting
Data base development and implementation
Workshop format and topic selection
Subcontractor coordination
Communication package: press release, newsletter, web site
Over 100 reagents acquired
Current Holdings:

- Antibodies (39)
- DNA Clones (21)
- Proteins/antigens (15)
- DNA Libraries (10)
- RNA (1)
- Mosquito stocks (19)

New Challenges

Biosharing: The changing environment of the ownership of intellectual property by individuals and institutions must be addressed

Bioinformatics: An information resource must be built to accommodate an ever-expanding volume of information. Unique attributes of this resource will be the linking of repository materials with specifically relevant data and providing tools for malaria research

Regulatory Compliance: The complex nature and sources of the repository materials requires vigilant attention to regulatory and ethical issues with overlapping levels of control

Summary

The repository is a significant step in tool development and capacity building in advancing malaria research, treatment, and control. Dr. Cypess described MIM delegates as the driving force for MR4 conception and development. He invited MIM participants to be active depositors and users and to participate in MR4 training programs.

"Librarians' Perspectives"

Useful partners in disseminating MIM reports AHILA, a brainchild of WHO library would be a useful partner in the dissemination of MIM reports. As a consequence, AHILA could be more

actively consulted for purposes of making MIM information widely accessible. Both the WHO libraries in Geneva and at AFRO have in the past been actively involved in feeding into AHILA health information of regional and global nature during AHILA congresses.

Listservs such as ahila-net@who.ch is useful to inform health information providers of the availability of MIM information. This service?s strength lies in the fact that AHILA has the capacity to disseminate health information to several African health institutions.

The health-l@zamnet.zm listserv for health care workers, which are moderated by WHO_ Zambia is another useful tool to inform people of MIM. It has been used to disseminate information on HIV/AIDS and other health issues since 1997.

However, neither web access nor any of the listservs can solve the problem of document delivery unless full documents are supplied on the systems. The African Index Medicus (AIM) and any other International databases have one handicap, that is the limitation to deliver full-text documents when and where they are needed within the shortest possible time. Where document delivery has succeeded, it has taken a lot of innovation and personal commitment on the individuals involved.

Normally, health libraries and institutions in developing countries do not have money to pay for health information and literature on the Internet. Therefore, serious consideration could be given to making MIM and other health information accessed through service organisations, both governmental and Non-governmental, that do not charge for information on their web sites.

Booth for Demonstration and Training

Conducted by South African MRC Representatives: Mrs. M. Mathys & Mrs. V. Thomas (ISD).

This booth demonstrated NCBI and PubMed services on the Internet as well as familiarized users with the African Health Anthology database. In addition, staff at the booth provided an overview of MRC's goals and research interests and promoted the MRC website and ISD services. A log of visitors to the MRC booth was kept which will be forwarded to the relevant NLM and NISC people. MRC staff will endeavor to do a follow-up exercise to ascertain delegates' progress in Medline searching and to render assistance where necessary.

Although levels of computer literacy varied from being non-existent to very sophisticated, the majority of delegates (in particular those from Africa) appeared to be technologically disadvantaged. Many of them have limited or no access to computer equipment. Clear evidence of this was noted on the final day of the booth's operation when delegates purchased disks so as to download the maximum number of references prior to departure.

A keen interest in PubMed and African Health Anthology was expressed by all those who visited the MRC booth. There was very little demand for the demonstration of NCBI. General information on the databases was given, followed by a search conducted by one of the ISD staff members. Thereafter, delegates were given the opportunity to search PubMed themselves on a topic of their choice, assisted and guided by an ISD staff member. What added to PubMed's appeal was free access. Delegates were also introduced to the comprehensive PubMed tutorial on the Web.

Dr. Barend Mons made use of the booth for demonstrating the SHARED database and printed material pertaining to the database was distributed from the booth.

In summary, the ISD staff proactively and adequately provided Internet tutoring, computer literacy training and facilitated discussion on health issues.

Communications Changes Perspective:

From Dr. Andrew Kitua, director of NIMR in Tanzania on the value of even rudimentary connectivity:

" . . . one specific story involves the Ifakara Centre. Before getting e-mail on HealthNet [a telecommunications service of SatelLife which provided limited access to e-mail], people were used to the telex and it seemingly worked well. But after we got HealthNet, things changed. Information access was faster and easier. It was like when a blockage in the water pipe is released. Last year, when there was a breakdown, there was an outcry like never before. Nobody wanted to go back to telex.

It makes a difference to be connected! We urgently look forward to full connectivity to the Internet through MIM's Communications Working Group, especially with regard to our regional malaria surveillance efforts."

From Dr. Yeya Toure, Director of the Malaria Research and Training Center in Mali on the value of full access to the Internet and the resources of the WorldWide Web:

"*What a pleasure for us and our collaborators to sit in our offices and browse the Web sites, being in contact with the world in a few seconds, looking for the hidden world. What a great potential we are discovering. I recently completed a proposal for TDR with six collaborators in three different countries. I could never have done this previously.*"

TECHNICAL APPENDICES

The objective of these appendices is to provide the reader with:

- an overview of technical information means by which an interested site representative can begin the process of getting connected
- an outline for what is required in terms of site documentation
- a step by step model demonstrating how one site got connected

Documents:

I. Outline site documentataion for site installation

II. Mali documentation – hard copy version with reference to website with hypertext links

III. Site visits

APPENDIX I. Installation of Internet Connectivity: Suggestions for Outline Documentation of a Site installation

1. Planning Phase

- Objectives of installation
- Definition of key deliverables
- Copy of IT strategy (if any)
- Overall approach adopted
- Documentation of existing computer infrastructure:
  - Hardware
  - Software
  - Network
- Notes on any regulatory issues faced and how they were overcome. Licensing required and costs.
- Notes on electricity supply.
- Changes required to existing infrastructure to cope with introduction of Internet access
- Copy of Project Proposals (if donors involved)
- Copy of Feasibility study (if any)
- Timeline: original proposed one and all deviations from it (plus reasons for deviation)
- Milestones
- Budgets: capital and recurrent
- plus depreciation costs
- for both upgrading existing infrastructure and Internet connectivity
- Sources of funding.
- Details of tenders / quotations obtained and company profiles
- Full specifications of VSAT (or alternative) equipment.
- Details of any changes required to building infrastructure.

2. Installation Phase

- Full details of equipment installed.
- Configuration of router(s).

- Configuration of server (s) providing the domain name service; routing; e-mail service; web proxy service. etc.. Hardware and software specification and details of all configuration steps and copies of files. Notes on backup procedures.
- Details of IP address allocation and domain registration. Note of how the Internet gateway is provided.
- Specification of Internet bandwidth provided and measurements of its operation in practice.
- Results of test over Internet link (as provided by installation company).
- Details of security surrounding the network (firewall protection from the Internet; anti-virus protection).
- If cabling was installed then test results from cable tests.
- Details of each computer that has Internet connectivity. Specifications; changes made to provide connection to the network / Internet. Operational software. User settings. Backup and security settings.
- Notes on use of consultants (if any). Their Terms of Reference and tasks undertaken, plus their reports.
- Copies of all correspondence with suppliers; internal agreements etc. (except where private).
- List of problems encountered and how they were solved
- IT staff. Their backgrounds and skills
- Details of staff involved in the installation.
- Reskilling and training of staff

3. Operational Phase

Sustainability plans

- Copy of Operations Manual for equipment and each user (where applicable)
- Integration of communications (with telephone system etc.).
- Communications patters: old and new and comparisons
- Statistics of traffic levels over the network and Internet connection. Details of peaks and troughs and indications of congestion. Analysis of sites visited (using proxy sever) and new communication patterns. Details of cost savings.
- Notes on staff uptake and further training / sensitization required.
- Details of support operation; help desk and network management.
- Set up for individual users. Software used. Standardization. Details of addressing. Opening web page.
- Any web design work
- Intranet details (if any)
- Integration into rest of management infrastructure and any other administration systems.
- Sources of literature accessed.
- Transfer of data: how it is done. Problems of standardization with other co-operating institutions.

4. Future Plans

- Upgrades to hardware / software required
- Upgrades to bandwidth envisaged.
- Notes on further web work now required
- Other future plans

APPENDIX II. Mali Documentation

Objectives of the installation of the Local Area Network and Internet access for the Malaria Research and Training Center (MRTC) at Bamako, Mali.

1. To give e-mail access to both the researchers and administrators at the MRTC for communication with other institutions in the world. Including visiting scientists involved in collaboration with the MRTC. With the advent of electronic communication it has become an essential tool in collaborative research efforts and grant proposals.
2. To give all nodes on the network access to the World Wide Web for both collaborative reasons, research purposes and literature searches. Again, some grant awarding institutions are moving towards online submission and review of grants. Without this access, it would put researchers in a location such as Mali who are without Internet access at a severe disadvantage in scientific research.
3. To build the infrastructure of the network and Internet access in a way the will reduce costs in both the long term and short term. Furthermore, the fault tolerance of the hardware and software must fit the environment and the lack of access to vendor support.
4. Teach the local support personnel to support the hardware and software including the network cabling, workstations, servers, wireless connections and routers.

Existing network and Internet access situation at the MRTC

1. Prior the installation of the current LAN several methods were tried for giving e-mail and Internet access to the MRTC. The first was through the SatelLife network. However, for various reasons related to the location of the laboratories next to a television broadcast tower the SatelLife antenna was unreliable and inconsistent. There was the added problem of the frequent visits by researchers from the NIH and other institutions where they were accustomed to high bandwidth Internet connections. When their e-mail was forwarded to the SatelLife addresses while they were doing research at the MRTC the high volume often clogged the connection and cut off e-mail for the entire site.
2. After the failure of the SatelLife connection for this site the Leland Initiative brought Internet access to Mali and four private Internet Service Providers (ISP) were licensed to provide access. It was decided to install a local area network and a dial up connection to the Internet using one of the local ISPs. The largest of the ISPs, Bintta was contracted to install the LAN and dial-up access. This was a unshielded twisted-pair network with 17 nodes in four buildings. The server was a Windows 95 computer running a POP server for email and a proxy server for web access. A simple 33.6Kbps US Robotics modem provided the internet connection.

· This solution was found inadequate for several reasons. First, the cost of the telephone bill given the local rate structure was found to be excessive and a drain on resources. Second, the low bandwidth and high latency of the connection allowed only one user at a time to browse the World Wide Web. Third, the POP server software was unreliable and frequently crashed or lost attachments, one of the most important needs of the scientists collaborating with institutions in the United States and Europe. Finally, the telephone service itself was unreliable and support from the local Phone Company erratic.

· The Leland Initiative offered to install a UHF connection to the ISP as a solution to the lack of reliability and high cost of the dial-up connection. However, the equipment provided for this connection was used and despite the best efforts of the engineers they were unable to establish the connection.

3. The solution decided on for these problems was to install a direct microwave connection between the MRTC and the ISP.
- The hardware selected for this solution was the Cylink 64SMP wireless microwave modems operating in the 2.4 GHZ band.
- The POP Server, the Windows 95 PC running the shareware application was to be replaced with a Windows NT server running Microsoft Exchange. The shareware proxy server would be replaced with Microsoft Proxy Server to route Internet traffic between the LAN and the Internet. This decision was influenced by the fact that since the computers were owned by the National Institutes of Health they would fall under the blanket licensing contract with Microsoft. Furthermore, the extensive experience that the National Institute of Allergy and Infectious Diseases (NIAID) had with both Windows NT and Microsoft Exchange as a Beta test site for both pieces of software. This would ensure a higher level of support from NIAID's network support staff, this institute has partnered with the MRTC since its founding.

Installation of the Local Area Network

1. The MRTC LAN was installed in 1998 by the largest of the local ISPs BINTTA with the financial assistance of the World Bank. It consists of 18 nodes installed at a total cost of $26,587. At least one of the nodes installed was faulty thus the cost was $1661.69 per node.
- It is an Ethernet network, twisted pair, 10BaseT Category 5 cabling using a 3Com 24 port OfficeConnect repeater as the hub.
- The LAN uses an invalid IP subnet because of the lack of addresses available to the ISP (Bintta has only half of a Class C subnet further subdivided for routing purposes). Thus, the POP/proxy server is the only node with a valid internet IP address.
- The connectors are all RJ-45 at the Wall Plates running to the telco Punchdown block.
2. This LAN connects the Parasitology, Entomology, and Hematology laboratories in addition to the office of the secretary general, the dean and vice-dean, chief financial officer and the Medical School library.
3. The entomology labs house the network hub and the server. The server as configured by the ISP to provide dial-up access to the LAN via a 33.6 bps. It was a Windows 95 computer running shareware POP/SMTP server and web proxy that allowed one node access to the web at a given time. There were no provisions made for backups and no training provided for support or administration to the medical school technicians.
- The server dialed up to the ISP over the semi-dedicated line. It was taken off-line when faxing was needed or if people needed to make local phone calls. This led to the server and network being off line frequently and sometimes the reconnection of the server to the phone line was forgotten leading to longer down-times.
- The server used PPP to connect to the ISP and a statically assigned IP address. The ISP provided store and forward email service.
4. The computers installed at the active nodes were provided by the National Institutes of Health, mostly Pentium and Pentium II Dell computers. The active node in the Library is connected to an IBM PC provided by the World Health Organization. The only active protocol installed on the LAN was TCP/IP. There was no printing over the network. All printing was done over parallel cables and parallel switch boxes for sharing.
5. The Windows 95 shareware proxy server allowed only web browser access to the Internet (no telnet or ftp) and only one computer at a time to access the World Wide Web and it was unreliable except on the server itself. Therefore, users and guest researchers were often using the server to access their e-mail via telnet or the web and browse the web.

6. Because there was no ftp access from the workstations virus information files for anti-virus software could not be downloaded automatically and many workstations became infected with viruses and passed them on to others. There was also no anti-virus software installed to check all incoming and outgoing e-mail attachments.
7. Furthermore, the e-mail server software frequently lost e-mail attachments, one of the most important features of the Internet for scientific collaboration.
8. The lack of training of the local staff meant that they were unable to test network nodes for wiring problems. Thus, those staff were unable to isolate the faulty node and tried replacing the NICs then the computer itself. The local ISP never returned to test or fix the problem.
9. This map of the LAN shows the topology after the installation of the Microwave link to the ISP. There are a total of 17 active nodes in the four buildings. One of the nodes in the Entomology building was faulty. This was subsequently replaced on the third visit by the local staff after they had been trained in cable manufacturing and testing.

What needed to be added

1. A network server was needed to handle e-mail traffic that would be stable, reliable, and easy to operate for the local staff.
2. This server must also act as a proxy server and route internet traffic such as World Wide Web, FTP, Telnet, and POP clients from the internal LAN to the ISP and the Internet.
3. A backup to the network server, to increase the level of fault tolerance.
4. The local staff needed to be trained in basic computer support, network support and operation.
5. The dial-up access to the Internet over conventional phone lines must be replaced with a more reliable and higher bandwidth connection. Moreover, the monthly charges from the phone company were prohibitive and competed with scientific research for scarce funds.
6. Therefore, the decision was made to replace this connection with a microwave link, this was influenced by the geographic location of the MRTC which is located at the edge of a plateau above the capital city of Bamako.

Installation Phase

The equipment initially installed:

- Primary Server: Dell PowerEdge SP5166 with 128 MB of RAM. This was intended to be the backup server to a new 333 MHZ Pentium II Dell PowerEdge however, the new server was seized by customs for 7 weeks and it had to be configured at a later date.
  - ◊ This server was running Windows NT Server 4.0 Service Pack 3.
  - ◊ The email software was Microsoft Exchange 5.5 SP1.
  - ◊ The Proxy is Microsoft Proxy Server 2.0
  - ◊ The network was reconfigured to run both NetBEUI and TCP/IP to improve the local ability and speed of sharing of resources such as network volumes and printers.
- Cylink 64SMP microwave wireless modem. Operating in the 2.4 GHZ frequency range at a potential data rate of 64 kbps and a range of up to 50 kilometers this served our purposes. The ISP would only offer us 56 kbps service.
- Eastern Research Router for WAN connections configured to bridge between the ISPs LAN and the MRTC using Point-to-point protocol. While routing would be prefered it was impossible to further subdivide the Class C that the ISP used.
- Two directional 30db microwave antennas connected to the Cylink by 50ohm coaxial cable.

The first problems encountered were the lack of unshielded twisted-pair cables. We had not anticipated the need to make both straight through and cross-over cables. It is necessary to be able to make cables at various lengths and types on site and not rely on local vendors, if they exist. Another problem is that the telco punchdown block installed by the local ISP is non standard for the United States where all the other parts and supplies originate. Therefore, we are dependent on that ISP for any additional drops that we wish to add. In future, it may be advisable to ensure that the hardware installed is standardized with the source of other supplies.

In fact, we were lucky that the previous attempt to connect Point G abandoned their cables because the antenna at the ISP had to be raised to a height of 12 meters, much higher than anticipated. The cable we had brought was not long enough and we used the cable from US AID. I think that in future it would be advisable to make the coaxial cables on site.

Another possibility for solving the cabling problems is to use a wireless solution. Wireless LAN recently dropped considerably in price and is more reliable than it was. There are two manufacturers that have good reputations, Arrow communications and Breeze Communications.

Some observations on alternatives

- Microsoft Windows NT 4.0 is a high performance operating system requiring a higher level of training than other Operating systems that could be used to do Proxy and Email for a network of this size. There are options for all other platforms that would be both cheaper and easier to maintain/support.
- Macintoshes are known for being very easy to use and there are several freeware applications that can be used to give a network both POP/SMTP electronic mail and proxy access to the internet. Apple Internet Mail Server (AIMS) is the easiest mail server to configure and maintain.
- Windows 95/98, has the noted advantage of being the most common operating system in the world and therefore reduces costs of training in many cases. Stability is not as good as the other platforms but there are many other advantages. Wide use translates into more software available at lower prices.
- Hardware compatibility not the issue that it is with both Windows NT and Macintosh.
- Linux, this operating system has many advantages including it being the most stable of the 4 listed operating systems. Software that performs all the needed functions is widely available and often free. Support is available on-line from many "non-traditional" sources.

Hardware list

- Dell PowerEdge 2300 server
- 2/4GB hard drives (Fast and Wide SCSI).
- DDS-3 DAT drive.
- 512 MB of RAM
- Dell PowerEdge SP5166 server (the Backup) ``
- 2/4GB Hard Drives (SCSI II)
- DDS-2 DAT drive
- 128 MB of RAM
- Cylink 64-SMP Wireless modems

- Eastern Research WAN routers
- 2 — 30dBi Directional Microwave dishes.
- 3Com OfficeConnect 24 port Hub
- 2 SMC Tiger Hubs, 6 Port (This part is no longer in production)
- 2 - 16 dBi Yagis (Omnidirectional Microwave antennas)
- 2 — Wi-LAN Hopper 30-24 wireless LAN Bridges
- 3 Mobiq Inmarsat M Satellite Telephones
- 3 Dell Latititude Pentium 266 Laptops
- Fluke LANMeter wiremapper.
- Twisted-pair cable making kit.

Software List

- Microsoft Windows NT 4.0 Service Pack 4
- Microsoft Windows 95/98
- Microsoft Exchange Server 5.5
- Microsoft Proxy Server 2.0
- McAfee Antivirus and NetShield
- ScanMail Antivirus for Microsoft Exchange Server
- On-Air Mobil software for Microsoft Exchange
- Microsoft Internet Explorer 4.01
- Microsoft Exchange Client for Windows 95

APPENDIX III. SITE VISITS

Purpose:

- Determine the status of connectivity at each malaria research site, and potential methods of providing it where it does not currently exist. Document and disseminate this information.
- Carry out feasibility studies, when requested, for the provision of Internet access to any MIM site. This to include costs and take into account local legislation and sensitivities
- Liasing with local and international Internet Service providers, as applicable to the technology to be introduced (VSAT, wireless, dial-up, leased line, packet-switching, etc.).

Regulatory Issues

Determine issues regarding legislation in each African country, and work to gain relevant permissions when required for the technology that is most suitable.
Assisting with obtaining the required licenses and local certification.

Equipment purchase and Installation

Determine best wireless technologies to be used. Reviewing topologies and costs, and negotiating with local ISPs (or other end connectors). Dealing with legislative issues. Procuring, delivering, and ensuring correct set-up.

Assistance with the procurement of hardware and software for connection. Following through with shipping and delivery and then providing a detailed plan for installation.

Testing and configuration of each VSAT system prior to shipment.

Ensuring that routing is correctly set up for all VSAT users. This may in some cases mean setting up DNS records, MX records and even a domain for sites that do not have existing external sites to look after e-mail and administrative issues.

IP address allocation where necessary.

Setting up e-mail addresses as required, and the establishment of a hosting body for e-mail (and web sites if desired).

Liaison with those who can provide installation services for all parts of the process of providing connectivity.

Operations - Technical

The control of bandwidth provided by the common satellite system to be shared amongst VSAT users. This will require monitoring of bandwidth used at each site, and ensuring that it meets demands and does not detract from other sites sharing the same bandwidth.

Liasing on upgrading of overall bandwidth to all sites, and on upgrading of bandwidth from each site to the Internet Gateway (which is related to the use and response at each site).

Dealing with the billing arrangements with the satellite users.

Upgrading bandwidth to the Internet itself (from the satellite groundstation).

Control of routing and remote maintenance of remote sites.

Renegotiating prices as and when they change (for satellite space; Internet gateway, etc.). Also re-determining prices for all sites under MIM when additional sites come on board or when bandwidth changes are required.

Reviewing new technologies as and when they develop.

Looking in particular at telephone-based technologies that may work jointly with Internet-based ones. This will include voice-over-IP (VoIP) as well as pure voice connections. Also negotiating for additional equipment or bandwidth that may need to be dedicated to this (or video-conferencing) on a short or long term basis at any given site.

Providing advice on the necessary changes to local computer configurations in the light of Internet connectivity. This would include the introduction of local area networks, upgrading of hardware and software (including introduction of servers and routers as required), and provision of security features.

Ensuring ongoing maintenance of all parts of the system.

Operations - Information

Liasing with those involved in production of information sources, and determining best policy on a front end to web access. This will include ensuring that all data / information flowing out from MIM sites is properly co-ordinated and published in a mutually acceptable form.

Liasing on the collection and maintenance of data across all sites, and advising on co-ordination and standardization.

Setting up and maintaining of newsgroups / list servers for all those with common interests (technical and research) across the MIM user community.

Recommend a policy on standardization of working practice and general software that will allow transfer of files between the MIM sites.

Ensure that minimal duplication of effort takes place between all sites, i.e. that there is horizontal asset integration.

Training

Establishing the availability of local training in both the installation and technical maintenance and the use of the Internet for communications and information access. Where local training appears insufficient, the co-ordination of specialized training to be provided by outside experts or via self-teaching material and especially written manuals.

Determining local staffing situations as regards ICT and proposing training and recruitment as appropriate.

Providing common workshops on technical and research / information based Internet usage as and when appropriate.

ETHICS AND RESEARCH METHODOLOGIES

Plenary Presentation

Ethics and Research Methodologies
Ogobara Doumbo

Breakout Session

Programme

Ethics and Research Methodology

PLENARY PRESENTATION

Ethics and Research Methodology

Ogobara Doumbo, Malaria Research and Training Center, Bamako, Mali

When I started to do science, I learnt a number of key things. One of these was that you need to consider ethical issues in everything; throughout the whole process of identifying a research question, developing research methodology, preparing a budget and finally analysing and interpreting your data. At each of these steps you need to think about ethics. Ethics in research is like a virus that infects your computer, and you have to be aware of it, otherwise the research programme, like your computer, will die. I would like to present to you today some experiences of Mali and Malians in tropical medicine research. During this research we have thought a lot about ethics, together with my colleagues.

In outline, I would like to present the study designs we are using in Mali and the associated ethical considerations; and then move on to compare informed consent in North America and Europe with that in developing nations. Finally, I would like to discuss the procedure used in Mali and some conclusions and recommendations.

Our first project is a study of the factors influencing whether infection leads to disease: why some children have mild malaria or severe malaria, while their brothers are running in the village. We set up a case control study in a cohort of 2,000 children at risk from malaria in a 10,000-inhabitant village. The study records the natural history of malaria to identify risk factors for infection or disease. Even though this is an observational study, you have to consider ethical issues. And because of the popularity of the cohort study in our domain, the villagers may see the physician many times, but in Europe if you are involved in these kind of trials, perhaps you meet the physician only on the first day.

In our second project we are studying gametocyte infectivity in the community by exposing experimentally infected gametocyte carriers to *Anopheles gambiae*. This is an intervention study because laboratory *Anopheles* are being fed directly on man. Such experimental infection generates many ethical questions.

The last design I would like to share with you is a community-based experimental intervention study. This study compares a weekly prophylactic to two doses of sulphadoxine-pyrimethamine in pregnant women. If you know the importance of pregnant women in the family in Africa, you will realise that you need to be extremely careful on ethical considerations.

Informed consent in Europe and in North America usual involves written documents, which the subject must read and sign in order to participate in a study. The emphasis is on the autonomy of individuals, equal participation of men and women, and a decision on the participation of children. The extensive legal language used to protect the investigator and the sponsoring agency is very complex. Literacy is rarely an issue in the North, but in our country Mali, or other parts of Africa, the situation is very different. In Mali, less than 20% of adults can read and write, and literacy is even lower in rural areas. The written document could potentially be discouraging for participation of the rural population, because they are not accustomed to this kind of thing. Signing documents is a daily event in the North: writing letters, transactions, credit cards and so forth. In contrast, signing documents in rural Mali is not an easy thing. People think twice before signing any documents, because it is usually linked to administrative issues. In addition, when I read ethical documents from Europe and America they emphasise issues surrounding individuals. However, in our country, it is the community and not the individual that is important. Even myself, I am not an individual in my village: I live in a community, and that is a very important difference in perspective to consider. Community involvement in informed consent is very significant in our country, compared with in America.

In the village you must first get a document signed at the community level, for example by the council of elders or women's organisation. After that you can move down to each family and then to each individual involved in your study. Discussions with individuals can then be in the context of the signed document from the community. You cannot jump directly to the individuals because they cannot do anything without community involvement. That is the real situation in Mali.

Legally, the equal participation of men and women are the usual things in Europe. Both ethically and biologically the particular case of pregnant women needs to be considered. In Mali in our Arabic community we have a very good representation of the women's association. Under the democratic system now, women are so active that there is a women's council in each village. These strategies have resulted in an increased understanding of participation in each kind of design now going on in Mali.

In the North, inclusion of children is not to be restricted because the target population for malaria is children and pregnant women. We need to think about our trials and to start to identify the population to be studied. I learned from working with Northern documents that for children the term 'assent' is used, because 'consent' is obtained through parents or guardians, and this is absolutely necessary.

I think, reading pages and pages of informed consent documents in the North, it seems this process is in the first instance tackling the investigator and protecting the sponsoring agency. The individual is left out because they do not always understand all those pages. It is a concern that pages and pages of foreign documents are not understood, because the language is so difficult. I am open for discussion on this.

In studies in rural regions of developing countries where medical care is limited, clinics can be set up to provide outpatient care for patients who are not directly involved in the study. This is a very important point because when I was medical student I saw villages participating in external studies, and when disease was found in the villagers the researchers would say that it was not their problem as they were just there to do research. This is not acceptable. But the other side is that establishing a clinic in a village can force the community to participate in your study. You have to be careful to balance the impact. And virtually all studies in developing countries guarantee to provide care for future complications related to the study because sometimes the scientific staff are only available in the village for one or two years. In villages where the study team is the only provider of healthcare, what choice do parents have if they have sick children and we are the only team existing there? We need to think carefully about forcing people to enter a study because we are also providing care. This ethical problem is not yet solved and is a big concern.

We have some mitigating factors. Observational study with no external intervention. The ability for overhead risk. Training and capacity development for the study and for vaccine study we need we have to avoid coercion before higher risk intervention studies are carried out. Individual consent in addition to community consent could be obtained now that we know. We also need a clinical trial monitor who can access local beliefs and attitudes. He needs to understand the social and cultural aspects of the area he is monitoring. For example, the with the structure of the Malian IRB; Professor Cisse the Chairman of the IRB community is a toxicologist and the Chancellor of a University. We also have representatives of the Supreme Court of Justice, the Women's rights activist, the Imaam of the big Mosque, the chief of the Catholic church, the dean of the National hospital and three faculty members - a gynaecologist, paediatrician and biochemist.

In conclusion, for me the key element of consent is that it needs to be informed, but it should not be have to be written. You need to take your time to inform potential participants properly and I would like to use the example of what we did when we set up our gametocyte infectivity study. The first time we presented our protocol to the community they rejected it claiming it was impossible to expose humans to Anopheles even if they were reared in a laboratory, due to the concern that they might be carrying a virus. We did studies to show to

the Committee that there is no evidence of this kind of virus coming from laboratory Anopheles. To convince the Committee it was necessary to go back to see the villagers. They stood in our laboratories in Bamako and asked our team questions and they followed the experimental infections we were doing feeding Anopheles in our laboratory. In this way we were able to convince them that if we bring a ten-year-old child from the village to Bamako he is safe, even if he is exposed to our Anopheles. Thus we took about three months to convince the villagers and no written document was used.

Informed consent must be based on a thorough understanding of the society in which the study is to take place. This is why we have our social anthropologist working with us every time to ensure that we understand the community well and get strong feedback. I believe that the process of consent in developed countries is now less informed than previously because it has been distorted by concern over legal liability. That is my thinking and it is open to discussion. In developing countries we need to think about the safety of individuals of the community and not only about protecting the scientist or the funding agency.

What kind of recommendation could we generate in societies where the authority is vested primarily in the community, as is the case in Mali? The initial focus and discussion should be with the leaders of the community, rather than individuals. By discussing directly with individuals you will introduce social problems in the village and this is unethical. Documentation should be available in the most common local language. You can translate English or French into this language and take your time to explain to the villagers so that they understand. They can then sign with fingerprinting as opposed to signing in written form so long as the document also has the fingerprints of the chief and leaders of the village. This kind of document is now permissible as a consent form.

Local communities participating in the study should have a council that includes both men and women so that both genders are equally represented in the decision-making process. In some villages only the men will talk with you, but in the background the women have control over the decisions. If you take time, the women in each village can give you a very clear and informed consent. Developing countries need to address the issue of legal liability in order to focus the process of informed consent on the study and its importance, significance and risk.

I would like to thank my social anthropologist and the Office of research. We have learned a lot from them because they send many documents to us and put pressure on us. Before starting any study they want to have IRB and those processes done. They listened to us because we said that we cannot accept all those big documents. You have to understand our culture. They took time to understand and accept the revised document that we sent back to them, and now we are in agreement. It is the first IRB committee to have been legally accepted by the minister of health and the minister for research and which now is registered at the US National Institutes of Health and different funding agencies.

I would like to thank all those villages where we have worked – it is not easy to work there, but if you get the confidence of the villagers, you can build a strong core study. I would like to say that in the cohort of children we are following in Bankoma we have 95% continuation rate after two years because of the time we took to convince the villagers and the confidence we gained from them. The work was supported by NIAID. Thank you very much.

BREAKOUT SESSION

Programme

1. Ethics and Research Methodology

Chair: Professor Brian Greenwood and Professor Ogobara Doumbo
Rapporteur: Dr Stephanie James

Introduction

Report of a workshop on ethics in clinical research in developing countries. - Brian Greenwood (10 minutes).

What makes research involving human subjects ethical? - Dave Wendler (15 minutes).

International ethical guidelines. Elucidation of major ethical principles; non-maleficence, beneficence, justice, autonomy (15 minutes).

Clinical research involving human subjects. Ethical question and design (15 minutes).

Appropriate design to answer relevant scientific question with relevance to health, including: conduct, feasibility, risk benefit ratio, population to benefit, results generalizable, reproducible - Wen Kilama

Informed Consent

Report of the workshop held in Liverpool 1998 - G. Malenga.

Individual vs. community informed consent - Marie-Pierre Preziosi.

IRB and national regulatory issues in developing countries.

Relevance, limitations and problems related to ICH guidelines in the developing world - Peter Folb.

Ethical reviews in overseas-funded research - Keith McAdam.

Summary and Conclusions - Ogobara Doumbo.

Summary Report: Ethics and Methodology of Research in Developing Countries

Chairs: Professor Brian Greenwood and Professor Ogobara Doumbo
Rapporteur: Dr Stephanie James

The various existing guidelines for conduct of clinical trials (e.g. CIOMS, Helsinki Declaration) were briefly reviewed, and updates given on other ongoing discussions (e.g. UK MRC Guidelines on Research in Developing Countries, Liverpool workshop on informed consent, US National Bioethics Advisory Council). Current thinking reflected in these guidelines was summarized into seven basic principles of ethical clinical research:

1. ask a valuable scientific question;
2. use valid and feasible methodology;
3. ensure equitable participant selection;
4. minimize participant risks while maximizing potential benefits;
5. conduct independent review;
6. ensure informed and voluntary consent; and,
7. demonstrate respect for enrolled participants.

With regard to the last point, the need to understand and respect local community culture was emphasized by several participants.
In this context, the interpretation of informed consent in the African setting, where the concept of community may be stronger than in Northern cultures, was discussed by several speakers. An example based on a study of a cellular pertussis vaccine in Senegal was offered to emphasize the benefit of taking a stepwise approach to informed consent, in which the study is first introduced to the village in a group setting before seeking individual consent. While this approach can be time-consuming and difficult, it was generally agreed that this was the best way to gain the trust and collaboration of the community. Other issues raised about informed consent in the African setting included the inherent concern about signing written documents, the problem of adequately informing people whose language and beliefs may not accommodate a medically oriented description of the methods and goals of a clinical trial, the question of how much information is adequate to get the message across (and who makes this decision), and the question of whether the potential trial participant perceives the informed consent process as an act of free will or views it as intimidating. It was suggested that follow-up after a study is completed could help to elucidate the answers to these questions, by determining the level of understanding which participants possessed going into a trial and whether they had any regrets about their participation after the fact. Such information could aid in the design of a more beneficial consent process in future trials.

Several discussants addressed other real-life dilemmas that face researchers. For example, in the design of a clinical trial when is the use of a placebo control group acceptable? Hypothetical situations were raised in which: 1) there is conflicting data on the value of the treatment under assessment; 2) the value of the treatment is assumed but not completely proven; or 3) the value of the treatment is proven under certain conditions, but not those which exist at the study site (i.e. in which local relevance remains to be demonstrated). No generalizable answers were offered, but alternatives to placebo-controlled trials (e.g. case control, historical control, stepwise wedge design) were introduced.

The role of Internal Review Boards (IRBs) was discussed. In general, IRBs are meant to perform as an advocate for trial subjects, in safeguarding their rights and safety. IRBs are meant to monitor any changes in clinical trial protocols. Yet even in relatively well financed institutions, IRBs are sometimes weak in fulfilling their mandate for ongoing review due to excessive workload. The need for adequate training for IRBs in developing countries was expressed, in order that they are prepared to understand and evaluate the risks and benefits of the proposed research. While IRBs in more developed countries may suffer from lack of understanding of developing country issues. IRBs in developing countries may suffer from

lack of knowledge of wider ethical issues. In both cases, IRBs must receive both education and material support in order to be effective.

Interpretation of the statement in the Helsinki Declaration requiring that study participants should be assured of the best proven diagnostic and therapeutic methods was discussed, and it was agreed that this should take into account the local standard of care, i.e. ethical judgements about care should be made by locally constituted ethical bodies and should be relevant to the country in which the trial take place.

In conclusion, it was agreed that no simple answers exist for many of the questions. There is a need for ongoing dialogue, in which he perspectives provided by scientists and lay individuals from developing countries are an absolute requirement.

WORKSHOP ON RESEARCH CAPACITY DEVELOPMENT IN AFRICA

Workshop Programme

Summary Report

MIM Workshop on Research Capacity Development in Africa, 19 March 1999

Programme

8:00 Objectives and expected outcomes – F. Zicker

8:15 Results from the MIM Review by the Wellcome Trust: – Pauline Beattie & Melanie Renshaw
- overview of funding opportunities, current malaria research infrastructure & activities in Africa;
- summary results of opinion survey on research training needs and solutions

8:45 Malaria research training opportunities and collaborations with the National Institutes of Health, USA. – Joel Breman

9:30 TDR Research Capability Strengthening programme - Fabio Zicker

10:00 Discussions

10:30 Coffee break

10:50 RCS needs and opportunities: a view from research institutions in Africa
- Malaria Research Centre (Mali) – O. Doumbo
- PIMRAT, University of Ibadan (Nigeria) - A. Oduola
- National Institute of Medical Research (Tanzania) – M. Lemnge

11:35 Discussion

12:00 Lunch

13:45 **Working groups** (6)- tutorial sessions on tips and tricks on writing-up research proposals; discussions on key issues of research design and implementation.

French speakers
A**.** Basic research and drug and vaccine trials - Y. Toure, J-F.Trape, P. Olliaro
B. Community-based interventions, socio-economic research - O.Doumbo

English speakers
A. Basic research – M.Troye-Blomberg and E. Ridley
B. Drug and vaccine trials – B. Greenwood and J. Targett
C. Community-based interventions -J. Kengeya-Kayondo
D. Socio-economic research - H. Mwenesi

17:00 Plenary discussion

Summary Report: Workshop on Research Capacity Development in Africa

Fabio Zicker, TDR, WHO, Geneva, Switzerland

The one-day workshop coordinated by the MIM/TDR Task Force on malaria research capability strengthening in Africa was designed to discuss needs, opportunities and different experiences for malaria research capability strengthening in Africa and to review methodological aspects related to development of research grant applications on malaria

The workshop invited registrations from African junior scientists, particularly post-graduate students, interested in enhancing their competitiveness in the area of protocol development and grant application who wish to discuss/review their own proposals with more experienced investigators; and from professionals involved in training, capacity building and collaborative research projects.

A total of 180 registrations was received, including professionals working in experimental research, product discovery and development, applied field research, socio-economic studies and control activities. Around 20 experienced investigators kindly helped to facilitate the discussions. The presentations and discussions focused on key issues related to malaria research project design and project implementation in different areas of expertise. The presenters were requested to explore the subject using concrete examples.

The agenda included three presentations from major funding agencies (Wellcome Trust, NIH and TDR) exploring needs, opportunities, and mechanisms of funding for malaria research and research training in Africa, especially those activities based on North-South collaboration. These presentations were followed by the report of 3 African research institutions (Malaria Research and Training Center, Mali, Postgraduate Institute for Medical Research and Training, Ibadan, and the National Institute of Medical Research, Tanzania) which described the process of research group development and international collaboration.

In the afternoon, six working groups were organized in parallel: 2 in French (around 40 participants) and 4 in English (around 140 participants). They covered the areas of basic research (laboratory research), drug and vaccine trials (preparing protocols to evaluate new products or to indicate an available product), community-based interventions (proposals that involve large number of participants such as bednet studies, chemoprophylaxis, vector control, etc.) and socio-economic research (health systems research, health seeking behaviour and studies on cost-effectiveness of interventions).

The group coordinators, with the assistance of experienced investigators (facilitators), reviewed key issues related to preparing malaria research proposals. The major objective of the working groups was to provide informal and practical discussions to strengthen the participants' capacity to prepare and submit successful grant proposals.

In some of the groups the facilitators used examples from current or past research projects and actively discussed with participants their projects. Among the topics discussed were: the definition of research questions, adequate scientific justification, coherence between objectives and methodology proposed, analytical approach, elaboration of a balanced proposal regarding objectives, time-lines and budget.

The workshop proved to be very useful in providing information on funding sources for training and research in malaria, scientific information on the web and for reporting experiences in international collaboration between African and non-African collaborators. The discussions on protocol design in different areas were very well received and elicited lively discussions. There was a strong recommendation to promote further such activities at different levels, particularly as satellite activities of major scientific meetings, varying from general broad scientific methodology workshops to more focused protocol development

workshops on specific areas. The agencies involved in the workshop were asked to consider funding of training on proposal development as a preliminary step for research capability strengthening.